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RECENT WORK ON INSULIN *

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INTRODUCTION

The discovery of insulin, which was reported some two years and a half ago, has been followed by publications from an extremely large number of investigators. It is interesting to note that many groups of workers have reported several times on this subject. It is quite obvious, therefore, that insulin is an interesting theme which is not easily exhausted. The large amount of literature which has accumulated makes it necessary to limit our discussion today to certain phases of the recent developments. It will be advantageous to dwell more particularly upon those aspects of insulin in which our laboratory is especially interested and which, at the present time, we are actively investigating. This will give me the opportunity of submitting to you the results of our recent experiments, as well as to review some of the published work of other observers. I shall try to touch upon phases of insulin other than those which have been very completely discussed in recent reviews.

THE PREPARATION OF INSULIN

The comparatively simple method for the preparation of insulin as originally published from Toronto (1) has been fol-

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lowed by the report of many modifications and improvements. At least twelve groups of observers have already reported on this aspect of the subject. I will not attempt to discuss the details of all the various methods, but you may be interested to hear in a general way of our experience with certain significant new developments.

The first solutions of insulin were made by watery extraction of pancreas. Alcohol was introduced as a solvent by the original investigators (2) and has remained the most popular extractive up to the present time. This solvent has been used continuously in Toronto in the routine preparation of material for clinical use, with the exception of a few months in the spring of 1922 when acetone was employed. Doisy, Somogyi and Shaffer (3) have used alcohol as the extractive in their method. These investigators introduced the precipitation of insulin from watery solution by half saturation of ammonium sulphate, and, coincident with Walden of the Eli Lilly and Company, the isoelectric method of purification. Fisher (4) has slightly modified this method by employing a higher concentration of alcohol than used by the previous investigators to fractionally precipitate the inert protein material. He claims to eliminate by this procedure a larger amount of those substances in the pancreas which antagonize the action of insulin. The existence of these substances was recognized very early in the work on insulin. Dudley (5) has retained the alcoholic extraction of the earlier methods as the first stage of his procedure for the preparation of insulin and has developed the so-called picric acid method of purification. In this method insulin is precipitated from watery solution, as the picrate, by the addition of picric acid. The picrate is subsequently treated with hydrochloric acid in 75 per cent alcohol and insulin is liberated as the hydrochloride. The hydrochloride is precipitated from alcoholic solution by the addition of ether or acetone. This method has been extensively used by manufacturers in England. Dudley (6) has recently published certain modifications of his method. He has obtained very satisfactory results by using alkaline alcohol as the extractive. Krogh (7), of Copenhagen, uses alcohol as the extractive. He believes that improved results are obtained when the glands are frozen as soon as possible after collection. The frozen mate-

rial is subsequently minced into acid alcohol. Robertson and Anderson (8) use alcohol as the extractive. They advocate the addition of sodium sulphate as a dehydrating agent, to the alcoholic filtrate from the glands. Moloney and Findlay (9) have recently published a second method based on the sorption of insulin. Charcoal is used as the sorper in this method.

Several groups of observers believe that water is a satisfactory extractive for insulin. Murlin (10) and his collaborators have used both alcohol and water as extractives. Using the latter, they have compared the yields of insulin obtained from the pancreas by perfusion, percolation and simple extraction. The fact that perfusion yielded the greatest amounts of insulin is of physiological interest. Dodds and Dickens (11) have reported the successful use of aqueous formic acid (1 per cent) as an extractive for insulin. These workers applied Dudley's method for the purification of the product. Very recently Dodds and Dickens (12) have reported favorable results with certain procedures which differ very considerably from their original method. The aqueous extraction is abandoned and extraction with acetone of glands which have been thoroughly minced and mixed with powdered picric acid, is substituted. We have been unable thus far to secure any better results with any of the above-mentioned methods than with the acid alcohol extraction method which we have used for the past half year for the preparation of material for clinical use. This method is essentially similar to that described by Scott and the writer (13). Detailed reference to the methods used in Toronto is given in this article. We find alcohol very strongly acidified with sulphuric acid, the most satisfactory extractive. The use of strong acid at this stage is advised by Somogyi, Doisy and Shaffer (14). In the search for better methods for the preparation of insulin many new properties of the substance have been discovered. This will undoubtedly result in the eventual development of very economical methods of production.

THE PROBLEM OF TESTING

Several methods of testing insulin are in use. The rabbit method is used by the Insulin Committee of the University of Toronto. A formula which facilitates the calculation of the potency in units per cubic centimeter is used. This method was

reported at the 1923 Meeting of the American Physiological Society by Orr of the Insulin Committee testing staff. The Unit as defined by the Committee is one-third the amount of insulin necessary to lower the blood sugar of a 2000-gm. rabbit, which has been starved 24 hours from the normal level to 0.045 per cent over a period of five hours. In our research work, whenever there is an ample supply of insulin-containing extract, we determine roughly the smallest amount of material necessary to lower the blood sugar of a 2000-gm. rabbit to about 0.060 per cent—that is, an amount which will produce an appreciable effect but not cause convulsions. We then administer a series of doses grouped closely about this roughly determined minimum dose to a number (6-10) of carefully selected rabbits. The rabbits are either absolutely fresh or have had at least a week of rest from use as test objects. The blood sugar is determined before and 1½, 3 and 5 hours after the injection of insulin. The unitage is calculated from the formula. The results are averaged and this value is taken as the unitage of the solution being tested. In testing a lot which is to be used in the clinic, from twenty to thirty rabbits are used.

The British Medical Research Council have used mice as test objects. Fraser (15), of the Connaught Laboratories, has published a method in which mice are used. The minimum dose required to produce typical convulsions is determined. Krogh, of Copenhagen, uses mice which are kept under standardized conditions such as temperature and diet. Although good results are claimed by individual investigators, difficulties have been experienced in co-relating the results of the different workers. Voegtlin, Dunn and Thompson (16) state that they have developed a reliable method for the standardization of insulin. The method is based on the lethal effect produced by insulin on "standardized albino rats kept under standard conditions of diet and atmospheric temperature." F. N. Allen (17) Department of Physiology, University of Toronto, has carefully determined the glucose equivalent of insulin on depancreatized dogs. The glucose equivalent was found to become progressively smaller as the dose was increased. Work of this type may provide us with an accurate method of assaying insulin. Finally, the clinical method of assay in the hands of expert clinicians

working on "pedigreed" patients has yielded fairly consistent results. Clinicians have detected variations of two or three units in potency. On the other hand, however, on certain occasions they have believed that they noticed a variation in the insulin when no variation existed. The difference was probably due to some changes in the clinical condition of the patient, of a nature too subtle to produce signs or symptoms. Nevertheless, the clinicians are the judges of our laboratory methods of standardization, and when our technique is good enough to produce lots so uniform in potency that they cannot distinguish between them there will be little cause for worry.

The Medical Research Council of Great Britain is engaged in preparing a stable insulin hydrochloride which after standardization may serve as the official standard.

YIELDS OF INSULIN

There are great variations in the findings of those investigators who have reported on the yields of insulin from pancreas. The variation is due partly to differences in the methods of testing, partly to the varying degrees of purity of the material under test, and only partly to the amount of insulin extracted from the gland by the method. It is impossible to evaluate a method when little or nothing is reported concerning the first two factors. Dodds and Dickens (18) report a yield of crude insulin of approximately 5500 clinical units per kilogram of pancreas. Moloney and Findlay (9) report the demonstration of 4400 units per kilogram of pancreas. Clough, Allen and Murlin (19) publish results demonstrating over 4500 units of crude insulin per kilogram. Dudley and Starling (20) obtain a maximum yield of about 1500 units of insulin, as finished hydrochloride, from one kilo of ox pancreas. Acid alcohol as used in our method extracts from 1500 to 2200 units per kilogram of pancreas. Consistent yields of 1100-1200 units of purified material (nitrogen 0.006 mgm. per unit) are obtained. In view of the variation in reported yields of insulin from pancreas, the matter might be simplified if the yield were always stated in terms of units of a finished product which has been found to be completely satisfactory in the clinic.

THE DISTRIBUTION OF INSULIN

In the search for the antidiabetic principle the pancreas has not been the only tissue investigated. The work of those who sought for this substance in blood will be familiar to you. Hédon (21), Hess, Forsbach, Alexander and Ehrmann, Drennan, Kramer and Murlin and others have studied the effects of transfusing diabetic animals with normal blood. Clark (22) has reported very significant results obtained by passing pancreatic perfusate through the isolated mammalian heart. Woodyatt and Raulston (23) were unable to observe any beneficial effect of the transfusion of normal blood to a severely diabetic patient. The recent work of Murlin (24) and his collaborators has been previously referred to in this communication. It should be noted that unsuccessful perfusion experiments have been recently reported by McCarthy and Olmstead (25) and that several groups of investigators have previously reported negative results with this method. There is no doubt, however, that this method has yielded very successful results in the hands of Clough, Allen and Murlin.

The method originally used for the preparation of insulin from the degenerated pancreas of the dog was not sufficiently delicate to demonstrate active material, in a convincing manner, in other tissues. The isolation of insulin from blood was reported from Toronto in May, 1923 (26). This, I believe, was the first report of the presence of insulin in tissues other than the pancreas. In Table I the report of an experiment in which an extract of blood was administered to a diabetic dog is summarized.

EFFECT OF BLOOD EXTRACT ON THE DIABETIC DOG

Dog. No. 18. Brown collie. Weight 14 kilos. Pancreatectomy performed September 17, 9 p. m. Dog was then starved.

The marked and characteristic response of this animal to the extract is convincing proof, in my opinion, of the presence of insulin in blood. You will note that a marked improvement in the general condition of the animal was observed, and that the liver, at autopsy, contained 5.85 per cent of glycogen. The typical insulin effect upon the blood and urinary sugar was

TABLE I

Date	Time	Blood Sugar %	Urine Vol.	Total N	Glucose Excretion	G/N Ratio	Injections	Diet	Remarks
Sept. 19	9.00 a.m.	0.236%						Starved.	
Sept. 20	9.00 a.m.	0.220%	355 cc.	11.0 gms.	34.1 gms	3.1		Starved.	
Sept. 21	9.00 a.m.	0.250%	355 cc.	9.9 gms.	32.1 gms.	3.2			
	11.20 a.m.						3 cc. sterile blood extract.		
	1.50 p.m.	0.268%							
	4.20 p.m.	0.256%							
	4.30 p.m.						4 cc. blood extract (Intrav.).		
	6.50 p.m.	0.205%							Animal very weak.
	9.20 p.m.	0.250%							
	12.00 p.m.						5 cc. blood extract (Subcut.).		Conjunctivitis both eyes.
Sept. 22	9.00 a.m.	0.224%	380 cc.	9.9 gms.	31.7 gms.	3.2			
	10.00 a.m.						15 cc. blood extract (Intrav.).		
	11.30 a.m.	0.230%							
	2.00 p.m.	0.224%					4 cc. urine extract, No. 261.		
	3.30 p.m.	0.224%							
Sept. 23	9.00 a.m.		190 cc.	5.8 gms.	17.9 gms.	3.1			
Sept. 24	9.00 a.m.	0.274%	375 cc.	10.9 gms.	41.4 gms.	3.8	3 cc. blood extract washings.		
	2.00 p.m.	0.148%							
	7.00 p.m.	0.180%							
	9.00 p.m.	0.218%							
	11.00 p.m.						4 cc. blood extract washings.		
Sept. 25	9.00 a.m.	0.167%	135 cc.	4.9 gms.	5.8 gms.	1.2			
	11.30 a.m.						5 cc. blood extract washings.		
	2.00 p.m.	0.079%							
	4.30 p.m.	0.048%							Animal in excellent condition.
	8.00 p.m.	0.085%							Eyes much improved
	12.00 p.m.						2 cc. blood extract washings.		
Sept. 26	9.00 a.m.	0.136%	185 cc.	6.5 gms.	Neg.	—		50 cc. weak insulin sol. stomach tube.	
	9.30 a.m.						4 cc. blood extract washings.	10 gms. glucose, stomach tube.	
	10.30 a.m.							¼ lb. beef.	
	11.30 a.m.	0.054%						50 gms. glucose, ¼ lb. meat.	
	4.30 p.m.	0.145%							
	9.30 p.m.						2.5 cc. blood washing.	¼ lb. meat.	
Sept. 27	9.00 a.m.	0.104%	350 cc.	6.3 gms.	Neg.	—			
	9.30 a.m.						6.0 cc. blood extract washing.		
	10.00 a.m.							50 gms. glucose, stomach tube.	
	11.30 a.m.	0.060%							
	4.00 p.m.	0.060%					50 gms. glucose (Intrav.).	¼ lb. meat.	
	5.30 p.m.	0.085%							

Animal killed 6.00 p.m., September 27th. The liver contained 5.85% glycogen and 12.76% fatty acids.

produced.* This extract was also administered to a number of normal rabbits. Characteristic insulin convulsions, which were permanently alleviated by dextrose, were produced when the dose was sufficient to cause marked hypoglycemia. A substance which consistently produces all these effects possesses the essential and characteristic properties of insulin.

Scott, Smith and I (27) have reported in detail on the presence of insulin in practically all the tissues of the body. We found insulin in the tissues of completely depancreatized dogs. Some of these animals were in the end stages of diabetes when they came to autopsy. Ashby (28) has been able to extract insulin from various tissues. He was not able to demonstrate any antidiabetic substance in diabetic tissues. Several European investigators have recently reported the presence of insulin in various organs. Very recently Vincent (29) reports that Dodds and Dickens have applied their revised method to the extraction of insulin from ox submaxillary gland and that a yield of 2130 units per kilogram has been obtained. Vincent states that "the fact that such large quantities can be prepared from a gland so like the pancreas in general structure cannot be without some fundamental significance. McAlpine in our laboratory has thus far been unable to secure yields from this source comparable to those reported by Vincent. McAlpine has used the revised Dodds and Dickens method. The significance of this active material in tissues other than pancreas is not increased in proportion to the absolute amount extracted by a certain method but depends more upon (1) the demonstration that the substance is insulin, and (2) the amount extracted by a given method compared to the amount extracted from the pancreas by the same technique. As we have reported elsewhere, thymus glands processed by our present methods are a much more fruitful source of insulin than pancreas extracted by the procedure originally used to prepare insulin for clinical use. The fact that the pancreas is far richer in insulin than any other tissue should not be overlooked.

There is still much to be learned concerning the distribution of insulin in the body, but I believe that we should await developments in methods of preparation and especially of testing

* A weak insulin solution, as noted in the table, was administered per os to this animal by mistake. A large amount of the potency was recovered from the urine. Numerous control experiments show that insulin per os does not affect the blood sugar or liver glycogen.

before a complete study which will necessarily require much time and expense is undertaken.

The exact significance of insulin in diabetic tissues is not known at present. We have made the obvious suggestion that the insulin must be present in a comparatively unavailable form. This is the only explanation, unless the generally accepted conception of the significance of the persistently low respiratory quotient in diabetic animals is doubted.

We have recently attempted to analyze the tissues of dogs thoroughly poisoned with phloridzin. Very little can be stated concerning these results as yet, but it appears that insulin is present in normal amounts in the pancreas and in demonstrable amounts, at least, in other tissues.

The bearing these results will have on the islets of Langerhans theory of diabetes remains to be determined. Although the great mass of pathological and physiological evidence supports this theory it has been vigorously attacked recently by Oertel (30) and by Vincent (31). These writers review work, mainly pathological, which leads them to the conclusion that the islets are not separate and distinct structures but are temporarily modified portions of the secretory tubules of the pancreas.

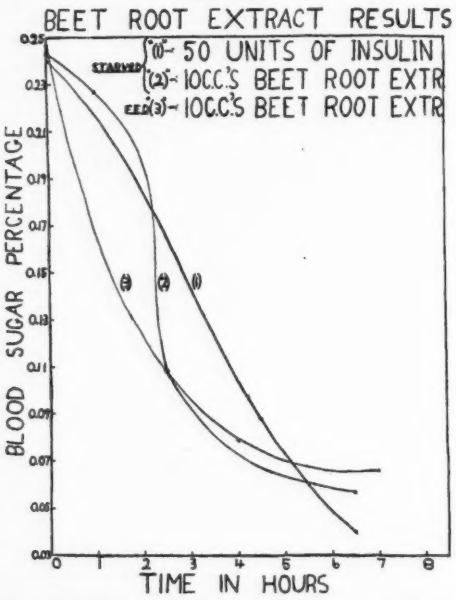
THE INSULIN-LIKE MATERIAL IN PLANTS

The literature dealing with the insulin-like material in plants has been briefly reviewed elsewhere (32). Macleod (33) points out that care should be exercised in considering these results since hypoglycemia may be caused by certain chemicals, by lowered blood pressure, by injury to the liver, or by stimulation of the pancreas. Stress has been laid on the delayed action of vegetable extracts by Collip and others. We submit curves showing the relative speed of action of a purified sample of vegetable extract as compared to that of an average dose of pancreatic insulin. In each of the three experiments the blood sugar had returned to its previous level by twelve hours after the time of the last determination shown on the chart.

You will observe that the beetroot extract exerts its effects on blood sugar as rapidly as insulin. The latter part of the experiment was conducted in the same manner as the early experiments by the Toronto group (34) when the effect of insulin on glycogen formation in diabetic dogs was being studied.

This diabetic animal was given large quantities of dextrose and beetroot extract. The liver at autopsy contained over 9 per cent glycogen. No pancreatic tissue was found. As our knowledge of the properties of this purified plant extract increases the similarity between it and pancreatic insulin becomes more marked. The yields of this active material from plants are very small

TABLE II



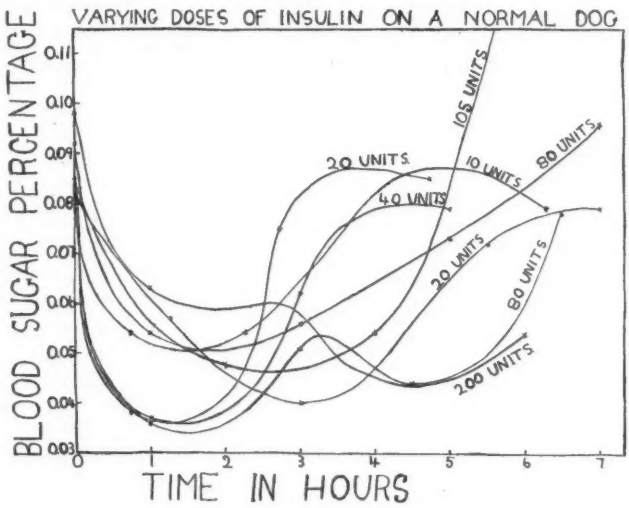
and the raw material is processed with much greater difficulty than is pancreas. The peculiar animal transfer phenomenon noted by Collip (35) remains as yet unexplained.

THE EFFECTS OF LARGE DOSES OF INSULIN ON DOGS

It has become apparent to many of those who have used rabbits extensively in testing insulin that a large dose does not invariably produce a greater effect upon an animal than a much smaller amount. This effect appears to be independent of the glycogen store of the animal at the time of the experiment. The work of F. N. Allen on dogs is interesting in this connection and has been referred to previously. Smith and I are engaged in a

study of the effect of large doses of insulin on dogs. As this work is by no means completed, I will present our results only very briefly. In Table III the effects of varying doses of insulin upon a normal dog are shown. This animal had approximately one week's rest between each two experiments. The animal was on a constant diet for several weeks before and during the experiments. The insulin was injected at the same time of day in each experiment. A study of the chart reveals the irregular nature

TABLE III



of the results. In some, but not in all experiments, we have noted a definite increase in the insulin content of the urine after large intravenous doses of insulin. In one experiment an animal was killed some four hours after a very large dose. Various tissues were extracted and the extract tested on rabbits. A definite increase in the insulin content of the kidney was found, but other tissues contained only normal amounts. However, it seems probable that insulin may be stored in the body since an animal may apparently completely recover from the effects but at a subsequent time exhibit hypoglycemia and convulsions. An animal occasionally exhibits this temporary recovery when dextrose is not administered. We hope that further work will

throw light on the interesting problems which arise from these preliminary experiments.

I am indebted to Miss J. Ridout, M. A., for her efficient assistance in connection with some of the experiments referred to in this communication.

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(DISCUSSION OF PAPER OF DR. BEST)

Dr. John R. Murlin, Rochester, N. Y.: Dr. Best referred to our experiments in extracting insulin by perfusion and percolation. He said we obtained a greater yield by perfusion than by the other methods. That was true until we found an improved method of simple extraction which we think is better, and which we reported in our last article. We now obtain more insulin by the simple aqueous extraction, using hydrochloric acid and heat, than we do from the same pancreas by either percolation or perfusion. The amount runs as high as 5400 units per kg. of pancreas. However, our comparison has been made only on the crude extracts. We have not given any figures on the yield of insulin in the refined form. The reason for this is that, as reported last winter in St. Louis, we have found a

form of insulin which seems to be entirely free from protein. Until our study of this product is completed we do not wish to say anything about the yield of insulin in a refined form.

In the experiments which I have reported today we used this crude form of insulin.

In brief the method which we have used since early last year is as follows: We make our extracts with heat, using about 1/5 normal hydrochloric acid and heating to about 75 or 80 degrees C. It does not seem to make any difference whether one heats just to that point or maintains the heat for 15 minutes or longer up to one-half hour. After cooling and stirring the material we neutralize to a pH of about 4. This neutralization throws down a heavy precipitate and gives a clear straw-colored filtrate. Re-extraction of this precipitate, however, gives a much larger yield. Combining the filtrates we next precipitate with sodium chloride, and it is this salt precipitate dried which we have used in most of the tests on oral administration. The salt precipitate usually gives about 3 clinical units per 100 mgs. dry. If we wish to use a stronger dosage we make a much more potent dry product by dissolving the salt precipitate in 70% alcohol, distilling off the alcohol and redissolving in 80% alcohol. This leaves behind the salt. After two or three such treatments every trace of salt is removed. From the final 80% alcohol solution we precipitate with 3 to 5 volumes of amyl alcohol. This precipitate when dry will keep indefinitely and retain its potency and it contains approximately one unit per mg. Of course it is not free from protein.

Some of the tablets which we have used in oral administration have been made by combining some of the amyl alcohol precipitate with the salt precipitate, thereby increasing the potency of the latter without materially increasing the weight. All our endeavor along this line has been to cheapen the production of insulin if possible, and to get it into form which may be administered by mouth.

THE CLINICAL ASSAYING OF INSULIN AND THE INSULIN REQUIREMENT *

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In a publication which appeared in the Insulin number of the Journal of Metabolic Research, I, with Boothby and others, proposed a clinical method for assaying insulin. Properly selected patients were placed on a standardized maintenance diet high enough in carbohydrate to cause slight glycosuria, and a value for the tolerance under these conditions was reached by subtracting the average daily glucose excretion from the glucose value of the foodstuffs metabolizing. The diet was then increased to a glucose value of 100 to 120 gm., and insulin (Eli Lilly Company) was administered in amounts such that glycosuria continued in about the same degree. The extra grams of glucose metabolized under these conditions divided by the number of units of insulin gave a glucose equivalent for different allotments with an average value of 1.5 gm. and extreme variations of 0.9 to 3.1 gm. While these considerable fluctuations were noted with different lots of insulin, the results with the same lot were fairly uniform in different patients. In the same number of the journal Woodyatt proposed a similar procedure and reached similar conclusions, namely, that with properly selected patients each unit of insulin injected subcutaneously provided an increased tolerance of from 1 to 1.5 gm. sugar. During the succeeding year careful tests were conducted in the Mayo Clinic on a large number of later lots of insulin (Eli Lilly Company) with more consistent results than we had previously obtained (Table 1).

In October, 1923, the strength of the insulin Lilly unit was increased, but since then we have not conducted a sufficient number of useful assays to permit an accurate comparison between the present unit and the previous one. From our less exact

* Read before the Association for the Study of Internal Secretions, Chicago, June 9, 1924.

observations, however, the present unit apparently has a value of about 2 gm.

The supposition that a quantitative relationship exists between insulin and glucose is supported by the experiments on animals by Frank N. Allan of Toronto, who used two totally depancreated dogs that were excreting sugar and obtained fairly constant results when constant experimental conditions were maintained. Furthermore, the glucose equivalent of insulin varied with the dose in an orderly manner which could be ex-

TABLE 1

CLINICAL ASSAYS OF INSULIN

Date 1923	Lot Number*	Assay	Date 1923	Lot Number*	Assay
Jan. 21	725737	1.6	Mar. 18	B 1460	1.3
24	725721	1.2	19	729780	1.7
26	725732	1.8	30	729777	1.9
27	725737	1.6	April 1	B 1464	1.7
Feb. 1	725745	1.7	5	B 1466	1.5
2	725740	1.6	13	729781	2.1
9	B 1438	1.3	13	729789	1.5
10	729748	1.9	15	B 1475	2.0
10	B 1439	1.6	15	B 1476	1.8
17	729748	1.9	26	733903	1.8
17	B 1440	1.6	26	729792	1.5
17	729752	1.2	28	733903	1.8
21	B 1442	1.2	30	B 1484	1.5
22	729753	1.9	June 1	B 1502	1.1
22	729752	1.2	21	B 1504	1.5
Mar. 3	729758	2.0	July 1	B 1514	1.5
5	B 1447	1.5	20	B 1521	1.7
10	729768	2.0	Aug. 1	B 1523	1.7
10	729759	1.2	16	B 1535	1.6
11	B 1450	2.0	27	B 1545	1.7
16	729775	2.0			
16	729774	1.5	General Average		1.65

* The lots prefixed with a "B" are lots sent to us by the Eli Lilly Company for testing clinically. The strength of these lots had previously been determined by physiologic assays conducted on rabbits. The lots with six-figure numbers were those distributed for clinical use after preliminary testing in various hospitals.

In September, 1923, an arbitrary revision was made by the Eli Lilly Company and the strength of their clinical unit was increased 40%. Since that time the glucose equivalent of the unit has been regarded as 2 gm.

pressed by an equation, although when the dose was constant the glucose equivalent increased with carbohydrate increments. Allan's conclusions that the level of the carbohydrate balance must be taken into consideration in judging the glucose equivalent of insulin clinically, is probably correct, but his assumption that we failed to do this is unjustified. All of our patients were essentially on the same carbohydrate balance and such fluctuations as were found in our early series of experiments can, I believe, be satisfactorily explained by the inconstancy in strength

of the different lots of insulin available during that early experimental period. Subsequently, as stated, the various allotments have behaved with much greater uniformity. We have yet to encounter such high glucose equivalents for patients as Allan reports for the depancreated dog, namely, 4 to 6 gm. of sugar for each insulin unit, but the condition of the two sets of experiments are not the same, and the fact that fairly uniform results were obtained both by Allan's method and ours is of greater significance than the disagreement as to the exact value of the glucose equivalent.

The subject is of some importance since it bears directly on the problem of how insulin acts. If a given quantum of insulin will always accomplish the metabolism of a definite quantum of sugar under fixed experimental conditions, the presumption is strengthened that the action of insulin is directly on the sugar. On the other hand, the absence of any rhyme or reason in the action of insulin would be evidence opposed to such an assumption.

The patients on our service receive diets that are closely adjusted to their energy requirements, and these diets are proportioned so as to contain relatively little carbohydrate and protein. With other regimes it is probable that the effect of insulin will be greater or less than we find it to be, and this indeed has been the experience of Allen and Sherrill. Furthermore, the presence of complications may have a very considerable influence on the glucose equivalent of insulin, as will be discussed.

Allen and Sherrill contend, if my interpretation is correct, that insulin not only favors the metabolism of glucose, but that of other foodstuffs. In other words, increased food calories of any kind, according to their experience, increase the demand for insulin, the effect of fat on the insulin requirement being more delayed than that of carbohydrate, so that it may be overlooked in short period observations. The chief objection to this conclusion is that it is based on the observation of patients who were for the most part emaciated and receiving very small diets. It must be admitted that patients who are underweight and receiving starvation diets can be given larger doses of carbohydrate than will be tolerated by the same patients after they regain weight, or when they receive adequate calories; also that small

doses of insulin appear to exert a surprisingly great influence on starved patients. I cannot believe, however, that the metabolic processes of such patients are directly comparable to those of normally nourished persons, and before attributing such profound effects as those observed to the often minute doses of insulin employed in their treatment I should like to be more certain how much of the effect observed is attributable to starvation. Joslin, for instance, infers that a false value may be ascribed to the insulin unit in undernourished patients, who, he says, are like his Mr. P. in Case 866, who was 50 per cent underweight, and had been undernourished so long that it required about three weeks to develop glycosuria, although the diet was considerably enlarged. Had this patient received 1 unit of insulin a marvelous effect would have been attributed to the unit. Furthermore, a number of patients with diabetes have been observed in whom protracted starvation had caused hypoglycemia, and in some of these carbohydrate, which was administered as a restorative, disappeared from the blood as effectively as if insulin had been injected. Our experience has been that fat may be added to the diets of well-nourished diabetic patients without appreciably increasing the insulin requirement. While we do not advocate excessive diets, nearly all of our patients are receiving high fat diets which amply provide them with calories for work. For farmers, the diets often total 2700 calories, and such diets have now been continued, in many instances, for more than a year and a half, yet the doses of insulin required by these patients are not in excess of those Allen and Sherrill are using, and the insulin requirement in most cases has remained stationary.

Heavy protein feeding is supposed to exert a deleterious effect on diabetes, and should therefore increase the demand for insulin. Petrén, in particular, opposes large protein allowances for diabetic patients, and Newberg and Marsh attribute the success of their high fat regime to its low protein content. In part the action of protein may be explained by its cumulative effect on the basal metabolism, as seemed to be evident in our severe case, Bessie B. During high protein periods the basal metabolism of this patient was increased 20 to 30 per cent, and the depressant action on tolerance was extreme and considerably

greater than that of isocaloric and isosaccharine diets low in protein. Protein, however, appears to have less effect on the basal metabolic rate and to be less injurious to patients with less severe diabetes who are able to store it in part and who can utilize the glucose derived from its metabolism. This at least is a conclusion suggested by the results of unreported metabolism studies conducted recently by Boothby and myself. Allen and Sherrill conclude, from their experience, that "a specifically powerful glycosuric influence of protein on the ground either of its specific dynamic or supposed toxic action are proved contrary to fact." This statement seems to me to be rather strong. It is true that they were able, in several cases, to feed very large amounts of protein provided the diets were low in fat calories with a beneficial effect on glycosuria rather than the contrary. Nevertheless, when high protein was combined with many fat calories, intense glycosuria was frequently provoked. Allen and Sherrill attribute this to the fat or total calories, but the experiences of others suggest that the share of the protein should not be neglected.

Acute diseases complicating diabetes often aggravate its severity and increase the insulin requirement. Among such complications are pregnancy, hyperthyroidism and infections.

Severe diabetic acidosis may likewise affect the value of injected insulin, although the evidence for this is not so conclusive. Diabetic coma is frequently precipitated by a complicating infection, and in such cases the infection rather than the acidosis may be responsible for the disproportionate insulin requirement. Uncomplicated cases of diabetic coma have not required insulin in amounts out of proportion to the sugar available for oxidation. In a number of such cases in the Mayo Clinic we have succeeded in controlling ketosis in every instance by doses of insulin not exceeding 100 units, which is about the requirement that might be predicted on the assumption that the unit has a value of about 2 gm. The body of the diabetic patient in coma is saturated with unused sugar. The blood usually contains more than 0.5 per cent of sugar, and it is highly probable that the tissues often contain more than 200 gm. Furthermore, small doses of carbohydrate are usually given in the treatment of this condition, and also when insulin is given in doses of 300 and 400

units daily for coma, as reported from several clinics, a large proportion of it may be excreted by the kidneys.

A patient who had pernicious anemia and diabetes died recently in the Mayo Clinic in diabetic coma. The patient's condition had not been unusually severe until terminally, after a precipitate drop in the blood count. She was at her home, and intensive treatment was not instituted until she had been unconscious for two hours. During the following ten hours 200 units of insulin were totally without effect on the blood sugar or acidosis. The combination of the two diseases is uncommon. I have seen it only twice, and Adams, who is reporting these two cases, informs me that he can find only one other instance in the literature.

Hyperthyroid conditions seriously aggravate the severity of pre-existing diabetes, and the insulin requirement of patients with abnormal basal metabolic rates rises and falls with the rise and fall of the basal metabolic rate. Whether the deleterious effect of hyperthyroidism is due entirely to the increased basal metabolic rate and the consequent necessity for more food, or is in part due to an antagonism between the thyroid secretion and insulin, is at present unknown. In one of our return cases (Case A105376) severe acidosis and threatening coma were twice precipitated by a sudden exacerbation of the hyperthyroid state, and very large doses of insulin (100 units daily) were necessary. We advise thyroidectomy in cases of exophthalmic goiter and of adenoma with hyperthyroidism, not only from the standpoint of the thyroid but because thyroidectomy, by reducing the basal metabolic rate, will lessen the food requirement and thus diminish the difficulty in managing the diabetes. Also, we advise thyroidectomy for diabetic patients with adenoma of the thyroid without hyperthyroidism, not on the supposition that removal of the goiter will benefit the diabetes, but merely as a prophylactic measure designed to protect the patient from the danger of hyperthyroidism later.

The most common complication in diabetes, and one that usually increases the insulin requirement, is infection. Numerous examples might be cited. As a rule, the more severe the infection, the more seriously is sugar utilization depressed, and the larger the dose of insulin necessary to prevent acidosis. In

several instances, with diets yielding not more than 40 gm. of glucose, 100 units of insulin were given daily. In the case of a child (Case A416633), 60 units a day were necessary, although before the onset of pneumonia the case was in a mild stage of diabetes and sugar-free without insulin. Sugar continued to be excreted, and it is probable that in this instance the glucose equivalent of the insulin injected was less than 0.5 gram for each unit. Epstein reported recently that the addition of trypsin to insulin neutralizes insulin almost instantly, in a medium too acid for the neutralization to be accounted for by proteolysis. It is possible that toxins and other infectious agents exert a similar neutralizing action on insulin, and that in this manner such complications reduce the diabetic's tolerance.

In early cases of diabetes great caution must be exercised in judging the effect of treatment because marked spontaneous improvement in tolerance may be encountered. Such a case may prove to be mild after a few days of dietary regulation despite an initial appearance of severity, and if insulin has been used the erroneous conclusion may be reached that a very few units have been responsible for a greatly improved carbohydrate metabolism. The ease with which early cases of diabetes respond to dietary adjustments is responsible for the deplorable success of quackery in this field. If a drug has been used it is improperly credited with the therapeutic success. Such cases, therefore, are not suitable for the trial of new diabetic preparations, and are equally unsatisfactory as test cases for gauging the glucose equivalent of insulin.

A similar situation is presented by the many patients with benign forms of diabetes, particularly those with arteriosclerosis or obesity. As Woodyatt has pointed out, they often reveal an extreme inconsistency between the richness of the diet in carbohydrate and the degree of glycosuria. With a diet of a glucose value of 100 gm. or less, 5 to 10 gm. of sugar may be excreted, and increasing the carbohydrate of the diet by 100 gm. or more will not significantly affect the intensity of the glycosuria. Such cases are obviously unsuitable for assaying the value of insulin. There remain, however, cases of moderate and severe diabetes in which the disease has existed for a year or longer and the patients are free from acute complications. In such cases, with

diets such as we have employed, insulin apparently behaves in a very precise manner, suggesting that a quantitative relationship exists between it and glucose. Age and the size of the body affect this relationship very little, if any; the unit of insulin behaves similarly in the child and the adult. The fact that uniform general metabolic conditions are necessary for uniform results should not, it seems to me, argue against the significance of such results. Chemical reactions usually require certain constant conditions. The purity of reagents is always a matter of concern to the chemist, and for quantitative yields reagents must be mixed in suitable proportions.

CONCLUSIONS

1. With uncomplicated cases of diabetes of sufficient duration the glucose equivalent of the Eli Lilly Company clinical insulin unit prior to October 1, 1923, averaged about 1.7 gm., when the diet was carefully adjusted to the calorie needs of the patient and carbohydrate and protein were limited. The material now in use has not been so carefully assayed, but from general clinical observation appears to have a glucose equivalent of about 2 gm.

2. The glucose equivalent of insulin may be altered by high protein and high carbohydrate diets, and the insulin requirement of the individual may be diminished by starvation.

3. The glucose equivalent of insulin is depressed by acute complications, especially infections.

4. The fact that consistent values for the glucose equivalent of insulin have been obtained under standard conditions with patients of different ages and weights, is evidence for the assumption that the action of insulin is directly on glucose and that a definite chemical interaction occurs between insulin and glucose.

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BRAIN DEVELOPMENT IN ANURAN LARVAE AFTER THYROID OR PITUITARY GLAND REMOVAL

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LOS ANGELES

This work is a part of a series of studies on the influence of the endocrine glands upon the development of larval amphibians. A general account of the brain of thyroidless R. pipiens larvae was given Allen '17. It was shown that this organ seen in surface view retains its immature condition in a stage corresponding with the degree of development of the hind legs and general body form. Even in tadpoles that had lived many months beyond the usual time of metamorphosis and had attained a size much greater than normal, the brain was found to correspond closely with the general bodily development. This early paper did not go deeply into the subject because a detailed study was left for a later time. The importance of this line of work is readily inferred from the fact that cretinism in man is so notably attended by mental deficiency.

E. R. and M. M. Hoskins '19 published views at variance with these, claiming that while there is a temporary retardation of the development of the brain to correspond with that of the body as a whole, nevertheless the later development of the brain brings it finally to about the condition to be found in the metamorphosed frog.

The writer has repeated his observations upon the surface appearance of a large number of brains of these thyroidless tadpoles ranging from a few months to as much as three years of age, but has failed even in the oldest to find any marked progress in brain development beyond that which corresponds to the general bodily development. There are certain special features that are distinctive, but they are not in the direction of development in metamorphosis. These will be discussed below.

The writer's study of transverse sections has proven to be especially instructive, showing clearly the undeveloped character of the brain in these larvae that are in so many other fea-

tures held in their immature condition. Similar observations, giving like results, were made upon the brain of Bufo americanus and were published in a preliminary account but are now furnished in full for the first time.

An article by Werner Schulze '24 fully substantiates these conclusions, "Gehrin und Rückenmark, des thyreopriven Tieres (tadpole) zeigen Organsysteme wie sie ihrem Bau und ihrer relativen Grösse nach für Larven charakteristisch sind. Aus dem Umstand, dass die Organe bis zu dem Tode des Tieres normal funktionieren, kann man ausserdem den Rückschluss machen, dass sie in ihrem Funktionszustand dem Larventyp des Tieres adäquat waren."

The material upon which this work is based was collected at Lawrence, Kansas. The fixing fluid used was bichromate-acetic. The thyroid and pituitary glands were removed at their inception by the methods explained in earlier papers (Allen '16, Allen '17). The tadpoles were reared under conditions of food and surroundings identical with those of the controls. The brains were dissected out, drawn with camera lucida, stained in toto in alum cochineal, and cut in serial section. The drawings of the whole brain were all made to a common scale and the sections were likewise treated uniformly on a somewhat larger scale. The transverse sections shown in the drawings and taken as a basis for comparison of the internal features of the brain were carefully selected to show corresponding regions of the brain, as follows:

1st. Immediately in front of the caudal point of union of the cerebral hemispheres;

2nd. Through the diencephalon at a point two-thirds its length behind its cranial end;

3rd. Through the center of the mesencephalon (optic lobes);

4th. Through the myelencephalon immediately behind the cerebellum.

The drawings were all made with the aid of camera lucida, with an aim to strict accuracy in the representation of relative size and general features of outline. The areas of nuclei are shown as well as possible, but such cellular details are only in few cases considered as a basis for the conclusions drawn. There

was little difference in the treatment of Rana and Bufo; save for the fact that in Bufo lateral views of the brains were included and a study was made of the brains of tadpoles deprived of the pituitary gland. See pages 644 to 651.

It is not necessary to enter into a lengthy description of the figures because they tell the story in themselves. We can gain our orientation from examination of the drawings of the whole brains of both Rana and Bufo. In the first place, there is a far greater difference in the degree of development of the brain of the thyroidless tadpoles as compared with that of the normal controls in the case of Bufo than in Rana. This is equally true when we compare the size of the body as a whole. This may be correlated with the clearly observed fact that the hind legs grow relatively longer in thyroidless and pituitaryless larvae of Bufo than in those of Rana. This has been interpreted as due to a greater tendency in Bufo to develop independently of these glands. The basic factors that control development, other than the endocrine glands, can carry Bufo further than Rana. It will be seen that this is not only true of limb growth, but that it is manifested in the development of the general form of the brain. The specimen of thyroidless Bufo selected for illustration and study was the largest and most highly developed of all, yet it still shows brain characteristics that are for the most part larval. This was a case of extreme development. A number of other brains of Bufo thyroidless tadpoles showed far more decided larval characteristics than this.

In the Rana pipiens and Bufo americanus the control larvae chosen for comparison were taken at a stage when the hind legs bear the same relation to body length that they usually have in thyroidless and pituitaryless tadpoles some months after the period when metamorphosis normally occurs. This is the stage with which we should properly compare the experimental specimens even despite the frequent differences in size. In Rana the differences between the brain of the control tadpoles of this stage as compared with that of the stage immediately after metamorphosis is very clearly seen. The young tadpole has rather weakly developed cerebral hemispheres, the diencephalon is narrow and elongated, the optic lobes are nearly hemispherical, and the fourth ventricle is elongated.

After metamorphosis the cerebral hemispheres are found to have elongated, the diencephalon has broadened, the optic lobes have become oval, meeting one another with their long axes at right angles. The fourth ventricle has become much shortened and the sides are rolled inward.

In the thyroidless tadpole the cerebral hemispheres, typically shorter than those of the normal tadpole, are dilated by the enlargement of the ventricles. The diencephalon is relatively narrower than in the metamorphosed specimens and more closely resembles that of the larval controls. The optic lobes are clearly like those of the normal larvae, and the fourth ventricle shows the same form. Certain special features are seen in the distended character of the cerebral hemispheres and the widening of the myelencephalon.

The pituitaryless tadpoles have brain features in every way comparable to those of the thyroidless specimens. There is little difference between them aside from the features that result from differences in size.

In transverse sections it is seen that metamorphosis causes a narrowing of the first and second ventricles. This is partly but not wholly due to the thickening of the median walls of the cerebral hemispheres. After metamorphosis there is a marked density of neuroblasts in this median thickened wall. The third ventricle is narrowed, its walls much broadened, and the nuclei embedded in them show a marked increase in number. Similar features appear in the optic lobes, while the myelencephalon becomes decidedly narrower and thicker.

In thyroidless and pituitaryless tadpoles the broadening of the cerebral hemispheres and the dilation of their ventricles is very marked. This is a constant character in all of the specimens studied. The diencephalon is in the main rather irregular in outline and the third ventricle is broader than in the metamorphosed specimens. In the brain of the giant thyroidless Bufo tadpole shown, this feature is less evident than in any of other specimens studied. Transverse sections of the optic lobes in the thyroidless and pituitaryless tadpoles show the same wide aqueduct of Sylvius seen in the larval controls. Finally, in the sections of the myelencephalon is seen one of the most constant and striking peculiarities, this structure being spread out

broadly with a wide open fourth ventricle. The walls are relatively far thinner than we find them to be in the metamorphosed specimens. While the resemblance of the myelencephalon of the speimens operated upon and the larval controls is unmistakable, the former yet have certain features that are peculiar to them, notably the hydrocephalous character of the cerebral hemispheres and the great breadth of the myelencephalon.

Cooksie '22 has shown that thyroid feeding causes the brain to develop toward the form found at metamorphosis. This is accompanied by decided deformity due to strong shrinkage of the brain case with little reduction in the size of the brain itself.

We might thus conclude that the brains of tadpoles from which the thyroid or pituitary glands have been removed tend to retain characteristics found in larvae of corresponding stages of bodily development. There are certain special features that mark them as pathological, but these are less significant than are the points of similarity to the larval conditions. The brain then follows the general rule so well illustrated in the other somatic organs that the tadpole retains its larval character both externally and internally when the thyroid gland or the pituitary gland is removed. While there are certain special features in these experimental tadpoles, the general conclusion given above is unmistakable.

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PLATE I.—SURFACE VIEWS OF BRAINS OF RANA PIPIENS. X-10.

Figs. 1 and 2. Normal control after metamorphosis. Total length 20.9 mm. Hind leg length 26.1 mm. Fig. 1, Dorsal. Fig. 2, Ventral.

Figs. 3 and 4. Thyroidless tadpole. Total length 88.7 mm. Trunk length 42.1 mm. Hind leg length 4.49 mm. One and one-half years old. Fig. 3, Dorsal. Fig. 4, Ventral.

Figs. 5 and 6. Larval control. Total length 63.7 mm. Trunk length 26.3 mm. Hind leg length 4.4 mm. Fig. 5, Dorsal. Fig. 6, Ventral.

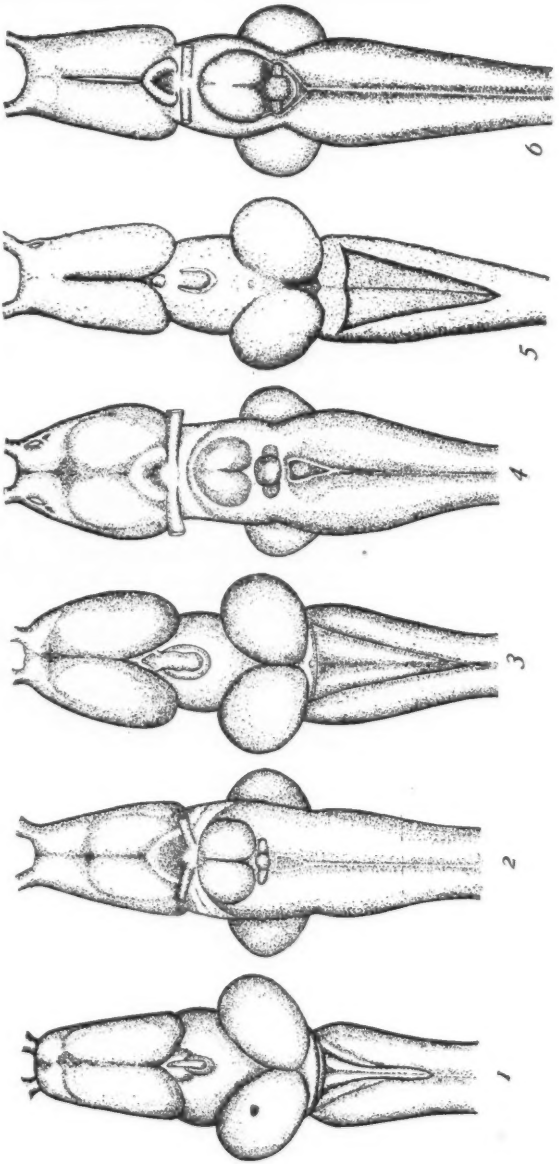
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PLATE II.—TRANSVERSE SECTIONS OF BRAINS OF RANA PIPIENS. X-15.

Figs. 7 to 10. Normal metamorphosed controls (shown Pl. I., Figs. 1 and 2). Fig. 7, Cerebral hemispheres. Fig. 8, Diencephalon. Fig. 9, Optic lobes. Fig. 10, Myelencephalon.

Figs. 11 to 14. Thyroidless tadpoles (shown Pl. I., Figs. 3 and 4.) Fig. 11, Cerebral hemispheres. Fig. 12, Diencephalon. Fig. 13, Optic lobes. Fig. 14, Myelencephalon.

Figs. 15 to 18. Pituitaryless tadpole (shown Pl. I., Figs. 5 and 6). Fig. 15, Cerebral hemispheres. Fig. 16, Diencephalon. Fig. 16, Optic lobes. Fig. 18, Myelencephalon.

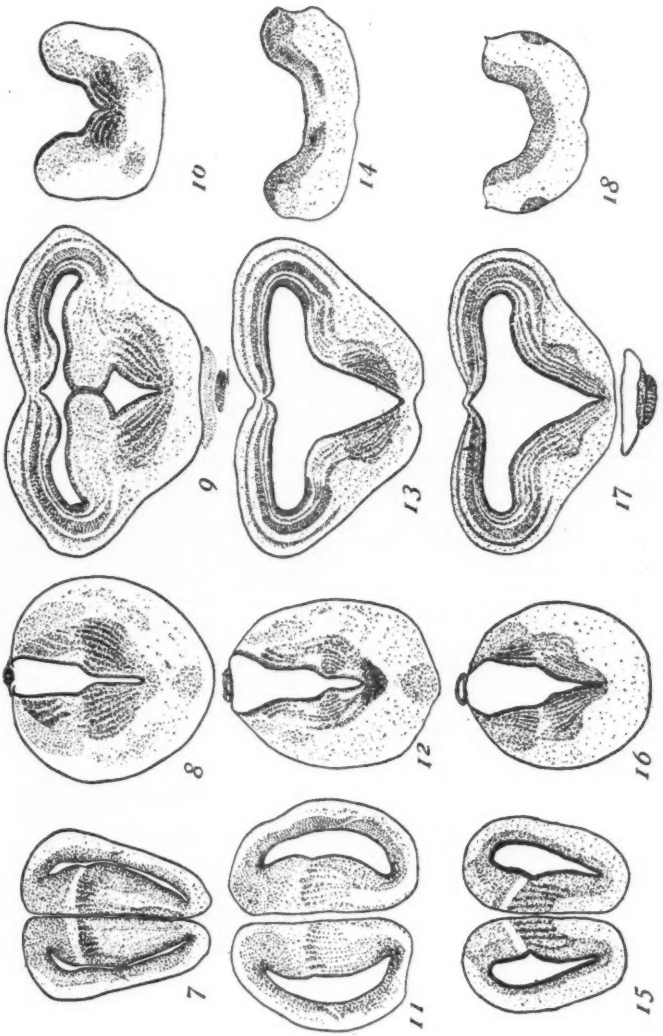
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PLATE III.—SURFACE VIEWS OF THE BRAINS OF BUFO AMERICANUS. X-10.

Figs. 19 to 21. Normal controls after metamorphosis. Trunk length 11.2 mm. Hind leg length 10.7 mm. Fig. 19, Dorsal view. Fig. 20, Ventral view. Fig. 21, Lateral view.

Figs. 22 to 24. Normal control tadpole. Total length 20.7 mm. Trunk length 10.7 mm. Hind leg length 7.3 mm. Fig. 22, Dorsal view. Fig. 23, Ventral view. Fig. 24, Lateral view.

Figs. 25 to 27. Pituitaryless tadpole. Total length 27.6 mm. Trunk length 14.6 mm. Hind leg length 3.6 mm. Killed May 17. Fig. 25, Dorsal view. Fig. 26, Ventral view. Fig. 27, Lateral view.

Figs. 28 to 30. Thyroidless tadpole. Total length 40.0 mm. Trunk length 19.7 mm. Hind leg length 4.88 mm.

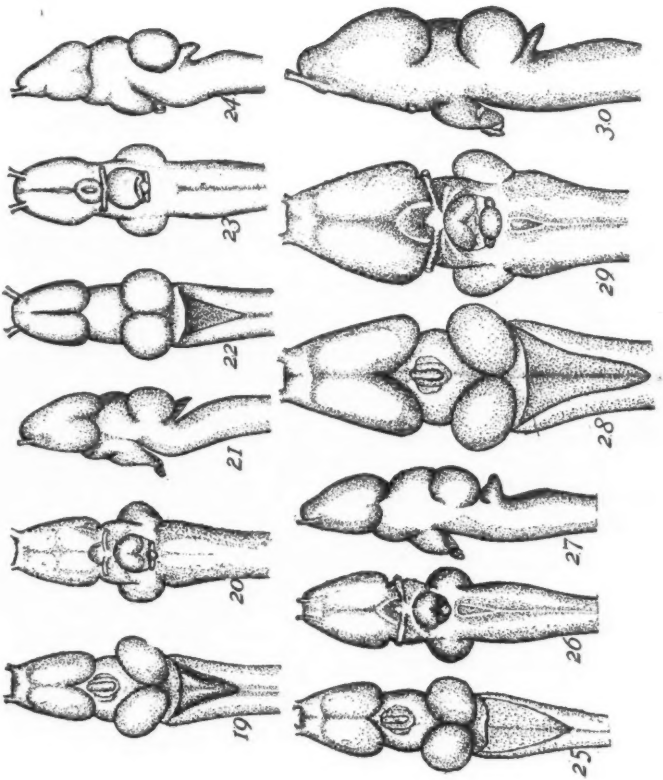
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PLATE IV.—TRANSVERSE SECTIONS OF BRAINS OF BUFO AMERICANUS. X-15.

Figs. 31 to 34. Normal metamorphosed controls (shown Pl. III., Figs. 19-21). Fig. 31, Cerebral hemispheres. Fig. 32, Diencephalon. Fig. 33, Optic lobes. Fig. 34, Myelencephalon.

Figs. 39 to 42. Pituitaryless tadpole (shown Pl. III., Figs. 25-27). Fig. 39, Cerebral hemispheres. Fig. 40, Diencephalon. Fig. 41, Optic lobes. Fig. 42, Myelencephalon.

Figs. 43 to 46. Normal control tadpoles (shown Pl. III., Figs. 22-24). Fig. 43, Cerebral hemispheres. Fig. 44, Diencephalon. Fig. 45, Optic lobes. Fig. 46, Myelencephalon.

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HYPEROVARIANISM AND ITS SPECIFIC TREATMENT

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OVARIES AND MENSTRUATION

Although there have been many noteworthy accomplishments in endocrinology, especially during the past two years, yet we know very little with regard to the functions of the various elements of the ovaries. Even concerning the causation of menstruation, which of course is the most striking of the phenomena by which the ovarian activity manifests itself, endocrinologists and gynecologists disagree, some following the opinion of Fraenkel, according to whom the menstrual cycle depends upon the corpus luteum; and others holding the opinion of Schickelé, recently accepted by Henry and Ramírez, according to whom the corpus luteum rather has an inhibitory action upon menstruation.

In an article published in this journal not long ago, Novak (1) of Baltimore said: "Again the studies of Fraenkel, followed later by those of Meyer, Schroeder, Ruge, and others, appear to have demonstrated conclusively that the corpus luteum is the element in the ovary which is responsible for the occurrence of the menstrual cycles, and the chronological relationships of the ovarian, endometrial and menstrual cycles have been quite satisfactorily worked out."

Blumgarten (2), of New York, still more recently states: "The importance of the corpus luteum in menstruation has been established."

On the contrary, Henry (3), of Paris, having studied the condition of the corpus luteum in different stages, found that: "Il y a des femmes régulièrement menstruées chez lesquelles on ne décèle aucun corps jaune en évolution." Holding the same view, Ramírez (4), of Mexico, stated that: "Not only does the corpus luteum have no function in initiating menstruation, but its presence impedes the menstrual onset."

HYPEROVARIANISM

Our knowledge of ovarian syndromes is likewise defective. It is true that we know well the symptoms (anovarianism) which follow ovarian extirpation, but we know only a little about the real ovarian insufficiency (hypovarianism) and still less concerning ovarian hyperactivity (hyperovarianism). I wish to point out that the existence of hypergenital syndromes has been denied even by Pende (5), who in 1915 emphatically asserted that "Sindrome cliniche di *esagerato sviluppo sessuale e di esagerata funzione sessuale*, dovute ad un processo morboso delle glandole genitali, noi non ne conosciamo."

However, if we review the recent literature on this subject, we shall find a few symptoms which may be referred to the hyperovarian syndrome. They are the following:

1. Precocious or excessive menstruation.
2. Uterine and mammary congestion.
3. Intermenstrual leucorrhoea.
4. Metrorrhagias.

Moreover, some cases of precocious puberty, genital hypersensitiveness, and exaggerated emotivity during the menstrual period, seem to be due to any disturbance of the ovary. However, the hypophysis and the thyroid may also have a part in the causation of these phenomena.

TREATMENT OF HYPEROVARIANISM

As far as therapeutics is concerned, we have no specific means for the treatment of ovarian hyperactivity. All the means which have so far been used for this purpose must be considered either palliative or even harmful. They may be arranged as follows:

(a) Chemical means: hemostatic substances.
(b) Physical means: cold applications; x-ray therapy.
(c) Mechanical means: ligation of the vessels; partial excision; total extirpation.

The use of hemostatic substances is empiric and usually proves to be harmful to the patient.

Cold applications as a symptomatic therapy are merely palliative. X-ray therapy must be used carefully and is to be

resorted to only when no other means succeed in bringing about the normalization of the ovarian functions. The chief disadvantage of this process consists in the possibility of definite degeneration or destruction of other ovarian elements which do not interfere in the production of the symptoms we wish to relieve.

Ligation of the vessels as well as partial excision usually fails.

Total extirpation must be condemned because the anovarian syndrome which results is more difficult to treat than the hyperovarian condition itself. When menorrhagia is caused by hyperfunction (dysfunction?) of the ovaries associated with other glands, the administration of either pituitary extract or pluriglandular extract (thyroid, pituitary, adrenal) usually succeeds, as has been recently shown, respectively, by Mossé and Fabre (6) and by Hartmann (7).

It was after thinking of the need of a specific cure for hyperovarianism that I, while in charge of the Organotherapeutic Department of the State of S. Paulo Serumtherap. Institute, decided to apply to the treatment of this syndrome the method developed by Moebius, in Germany. This was developed for the treatment of Basedow's syndrome and consisted in the use of the serum of thyroidectomized animals. To be sure, Moebius' point of view has not been upheld, and serum prepared according to his principle has, as a rule, proved unsuccessful. It now appears, indeed, that Basedowism is a form of dysthyroidism or of pluriglandular dysfunction rather than of hyperthyroidism as Moebius supposed. I think, however, that the first results which I have obtained from the application of the same principle in the treatment of hyperovarianism are somewhat encouraging.

My process consists in the use of the serum of animals (ewes and she goats) aseptically ovariectomized. The first bleeding is done about 20 or 30 days after the operation. The serum is administered either *in natura* by injections or with 40 per cent neutral glycerin by mouth. The action of this serum was first tried by Dr. V. Brazil, the former director of the Serumtherapeutic Institute (Butantan Institute), on a relative of his, who suffered from hypermenism and showed exaggerated emotivity during her menstruation. In this case glycerinated

serum was given during the patient's intermenstrual periods and was successful.

The serum was further applied by Drs. C. Garboggini, A. V. Marcondes, C. Bourroul, and A. Fagundes, and myself in S. Paulo, Brazil.

My own observations are as follows:

Case 1. O. D., 24 years, white, living at Butantan (S. Paulo, Brazil), began menstruation at 12 years, married since 1917, had 2 children. She suffered from menorrhagias that lasted about 9 days and sometimes relapsed during her intermenstrual periods; there was also intermenstrual leucorrhea. Glycerinated serum of ovariectomized ewes was given by mouth during the intermenstrual period for 5 months. Recovery took place. (March, 1922.)

Case 2. L. G. P., 18 years, white, living at Butantan, began menstruation at 12 years, married since 1918, and had 3 children. Menorrhagias lasted 7 days and sometimes more; there was genital hypersensitiveness. Caprine serum (from ovariectomized she goats) was given subcutaneously, 10 cc. daily for 3 days at 3 premenstrual periods; the second application was followed by mild urticaria; the patient was desensitized by Besredka's method before the third application. The patient recovered. (April, 1922.)

Case 3. A. C., 21 years, white, single, living at the village Pinheiros, near Butantan, began to menstruate at 13 years. There were menorrhagias for 6 to 9 days with nervous erethism and eruption of facial acne at the premenstrual period. Ovine serum was given subcutaneously, 10 cc. daily for 5 days, before the menstruation. Preventive serum desensitization was practiced at the second application, which was followed by recovery. (June, 1922.)

Case 4. D. M., 18 years, colored living in the village Pinheiros, began to menstruate at 11 years, married early in 1921, and had no children. She had menorrhagias for 9 days. Glycerinated serum was given by mouth, 3 teaspoonfuls daily for 5 intermenstrual periods. There was apparent betterment, consisting in the shortening of the menstrual period to 7 days. (July, 1922.)

Case 5. M. G., 14 years, white, single, living in Conchas (State of S. Paulo, Brazil), began menstruation in 1920. Menstruation lasted 10 days and was preceded by painful uterine congestion. The same phenomena were observed at four successive menstruations. Before the fifth menstruation glycerinated ovine serum was given by mouth, 3 teaspoonfuls daily for about 12 days. Menstruation became painless and shortened to 6 days. Early in 1922 the phenomena of hyperovarianism appeared and the serum treatment again resorted to was successful. (Dr. C. Garboggini's observation.)

Other cases. Shortly before leaving for this country, in August, 1922, I was informed by Drs. V. Marcondes, C. Bourroul and A. Fagundes, who were using the serum I had given them in their gynecological clinics in S. Paulo and who had already applied it to 8 patients of their own, that it was proving successful.

The usefulness of the serum of ovariectomized animals on patients of hyperovarianism may be explained by admitting that such serum, lacking ovarian hormones and probably being rich in hormones from the thyroid, hypophysis and other glands which apparently have a part in the production of the oestrual

changes, may excite these glands when they are in a condition of deficient activity, as seems to be the case in hyperovarianism, thereby establishing the hormonic equilibrium.

By giving this paper for publication I wish not only to call the attention of all those who are interested in the further development of the methods of treatment of endocrine diseases to the action of the serum of ovariectomized animals, but also to ask their co-operation in the solution of this new endocrinological problem.

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PARATHYROID TETANY *

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The parathyroid glands have long been regarded as internal secreting organs, whose product plays an extremely important part in metabolism and whose absence quickly leads to the death of the individual in profound depression or more commonly in a state of great nervous excitation, the so-called parathyroid tetany. The recent development by the author and his associates (1) and by Luckhardt and his co-workers (2) of several methods by means of which this post-operative depression and tetany may be entirely prevented and controlled has brought out the important fact that dogs may be kept alive for years and perhaps a normal life span with no trace of parathyroid tissue, as at present defined, in the body. This statement is made with a full realization of the demonstration of supernumerary and accessory parathyroid glands in a varying per cent of animals in different species, and I believe it to be a fact. Every investigator who has worked long in this field has met with animals which showed neither tetany nor depression after what was supposed to be a complete parathyroid extirpation and which survived indefinitely thereafter in good condition and free from tetany. Such occasions are not many in the dog but vary greatly in other species. In many of these survivors accessory parathyroid tissue has been found in the neck, in the thymus, or along the trachea, aorta or pulmonary artery. When, however, the thyroid and parathyroid glands in the dog are widely extirpated and no glandular tissue is left in the neck, not more than five or ten per cent of these animals will survive more than two weeks without treatment. In my experience of over one hundred thyro-parathyroidectomies in the dog, only three per cent survived. Simpson (3) reports no survivals, in over one hundred complete operations. The literature on this point is not very val-

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uable since not many authors have operated upon enough dogs to make their statistics significant. Those in which authors claim to have removed all the parathyroids leaving the thyroids intact should not be considered, because of the great probability of some parathyroid cells remaining imbedded in the mass of the thyroid glands which were left. When, then, it is possible by the method of treatment to be described below to preserve from 75 to 90 per cent and perhaps more of dogs from which both thyroids and parathyroids in the neck have been removed, the significance of these methods cannot be doubted.

One may, however, still argue—and some (4) apparently prefer to do this—that all dogs have accessory parathyroid tissue some place in the body. This assertion cannot be disproved, but it would be still more difficult to prove it. One might conceivably make serial sections of the entire animal and examine these painstakingly under the microscope for cells that histologically resemble those of the parathyroid gland. But if they were found it would still devolve upon the investigator to prove that they were functionally identical with the glands in the neck.

In a report before this association in St. Louis two years ago I described a method by means of which male and non-pregnant female dogs could be kept alive and free from tetany following complete thyro-parathyroidectomy. The principle of the method involved the prevention of bacterial proteolysis in the intestines by special diets. These early experiments have been confirmed and amplified, and we may now definitely say that over 90 per cent of completely thyro-parathyroidectomized dogs may be kept alive by this method. At about the same time, Luckhardt found that similar results could be obtained by an entirely different method, namely, the intravenous injection of large amounts of Ringer's solution. Some time later Luckhardt and Goldberg found that the oral administration of calcium lactate in large amounts was quite as effective in the control and treatment of parathyroid tetany as the two previous methods.

While the interpretation of these findings is perhaps unsettled, their accuracy and great significance cannot be questioned. At the present writing we have treated eighty dogs in which a complete thyro-parathyroidectomy had been done, by either one or a combination of the methods described above.

Seventy per cent of these have survived for two months to two years. Included among the 30 per cent that died within the two-month period are those killed by accident or which died from intercurrent infections. Such a large percentage of recovery cannot be explained on the basis of the presence of accessory parathyroid tissue, as at present anatomically and physiologically defined.

If a ten-kilogram male or non-pregnant female dog be placed on a diet consisting of 75 grams of lactose, 500 cc. of milk, and white bread ad libitum per day, tetany or depression will not develop following thyroid and parathyroid removal. It was found advisable to continue this diet for two weeks before operation, when the feces became liquid, colorless, acid to litmus, and the fecal bacteria predominantly aciduric in type. After operation the animal was fed daily with the stomach tube for at least a month. Such a dietary regimen checks bacterial proteolysis or putrefaction in the intestinal tract and accordingly prevents the formation of the highly toxic protein derivatives commonly resulting from such action.

It has been demonstrated by the author (5) that the toxicity of the intestinal content depends in largest part upon these toxic protein derivatives arising from bacterial proteolysis, and the interpretation placed upon these experiments depends upon this fact. Parathyroid tetany is an intoxication and the responsible toxic substances come chiefly from the gastro-intestinal tract. The discovery by Luckhardt and Rosenbloom that parathyroid tetany or depression can be entirely prevented or controlled by the daily administration of large amounts of Ringer's solution intravenously is in harmony with this view. The vigorous diuresis induced by such injections might well remove from the blood the toxic materials responsible for the tetany. This explanation has, however, lately been modified by Luckhardt and Blumenstock (6) through the realization of the role played by calcium in Ringer's solution. Other solutions, free from calcium but producing greater diuresis than Ringer's solution were not quite so effective in controlling the tetany. The relief that may be obtained by the intravenous injection of calcium lactate in a dog in violent parathyroid tetany, as demonstrated by McCallum and Voegtlin and others, is indeed, as Berkeley and

Beebe remark, "one of the most striking in the range of physiological experimentation."

The fact, however, that parathyroidectomized dogs may be kept alive and free from tetany for indefinite periods by the daily oral administration of 20 to 30 grams of calcium lactate is perhaps of still greater significance. The role played by the calcium is not readily understood. At the present time it cannot be said with certainty whether the calcium supplies a specific physiological deficit in the organism or merely controls the syndrome of parathyroid tetany by its pharmacologic action. The latter possibility becomes more evident when it is realized that if the parathyroidectomized dog is carried safely through the first six or eight weeks by any one of the three methods, he may thereafter survive in good condition without further treatment.

The prevention of parathyroid tetany by checking bacterial putrefaction in the gastro-intestinal tract indicates certainly that this must be the chief source of the tetany poisons in male and non-pregnant female dogs. Tetany in pregnant dogs cannot, however, be controlled by this method. It can, however, by the intravenous injection of Ringer's solution, and it appears very probable, accordingly, that during pregnancy poisons, capable of causing tetany, may arise elsewhere. The available evidence indicates that the pregnant uterus may supply such toxic materials, and in this sense tetany may be considered as one of the possible toxemias of pregnancy. Parathyroid tetany in pregnant dogs may also be prevented and controlled by the oral administration of calcium lactate. Larger amounts are necessary than suffice for non-pregnant animals. Thus, if this calcium salt exerts an antitoxic action, its influence is not only local but must extend also to poisons in the blood stream.

Oestrus and lactation are likewise special conditions during which tetany may appear on parathyroidectomy, even if all bacterial putrefaction in the gastro-intestinal tract has been prevented. This tetany may, however, be controlled by the intravenous injection of Ringer's solution or the oral administration of calcium lactate. It is possible that the changes in the uterine mucosa during oestrus may occasion the local production of toxic substances which enter the blood stream and cause tetany. The withdrawal of calcium in the milk, however, is certainly a factor

which must be considered in the pathogenesis of the tetany of lactation.

A complete analysis of the pathogenesis of tetany must take cognizance of the facts indicating the presence of an intoxication and also of the facts developed with regard to the role of calcium and perhaps other inorganic salts in this condition. There are no facts irreconcilable with the view that tetany is a toxemia, and there is much evidence to support it. The control of tetany by certain calcium salts does not disprove this view and when more is learned concerning the action of calcium it is probable that the apparent contradictions will vanish. It is not probable that the toxemia is due to any one chemical substance, or indeed to the same substance in all species of animals. The chief source of these toxins in the dog and probably also in all carnivorous animals is bacterial putrefaction in the intestinal tract. They may, however, also come from the uterus in pregnancy or from bacterial products in case of infections. We have not yet secured definite evidence of their endogenous origin, that is, as a product of normal cellular metabolism.

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(DISCUSSION ON PAPER OF DR. DRAGSTEDT)

Dr. Arno B. Luckhardt, Chicago: The methods employed by us in the investigation of the prevention and possible cause of tetany are quite different from those fundamental considerations which prompted the experimental work of Dr. Dragstedt. It is an interesting thing that in spite of the fact that the basis of the experimental work is entirely different, the interpretation of the results is almost identical. I am in thorough agreement with Dr. Dragstedt that the cause of tetany is intoxication, that it is not a diminution of calcium *per se* or what might be called a hypocalcemia.

As outlined by him, our methods were the intravenous injection of a solution of calcium which we are told would be ineffective. Just

how the administration of calcium keeps the animal normal after parathyroidectomy is not quite clear. We started with the administration of calcium lactate, but recently, in the past six months, decided to test out the efficacy of other calcium compounds, and Mr. Tumpeer and myself tested out calcium acetate and calcium phosphate. These are quite as efficient as calcium lactate except calcium phosphate. Calcium phosphate, when given in quantities by mouth, rather predisposes to the onset of tetany rather than cures it. There may be some relation between the injection of calcium phosphate and the more rapid absorption. Tentatively, I have assumed that the hypocalcemia described in tetany is rather the effect of the tetany than its cause. The calcium compounds might be acting in the gut by changing the metabolism of these protein products as Dr. Dragstedt said. Calcium might act in the gut by neutralizing the hypothetical toxins which are supposed to be responsible for the tetany. Calcium is known to change the permeability of the gut. If that were the explanation these hypothetical compounds might not be able to pass through the gut and could accumulate in the tissues and in the blood stream and thus predispose to tetany. That the permeability of the gut is a factor in the genesis of tetany is evidenced by the findings of Tumpeer and myself as indicated by the fact that any maneuver to change the permeability of the gut will promptly throw the animal into tetany. We worked on animals that had survived complete thyroidectomy for 40 to 60 days. We put them on a specific meat diet which was supposed to produce tetany and they did not develop it. By giving a brisk cathartic to produce an enteritis and change the permeability of the gut we were able to throw these animals into tetany later. That tetany was promptly controlled by the thorough administration of calcium compounds, except phosphate. That observation would support the view that the calcium compounds act in the gut by makit less permeable. We can assume that a change in the permeability following the removal of the parathyroids leads to a greater excretion of the gut, that the removal of the parathyroids permits circulation into the gut with greater ease. It is known that the chief route of excretion of calcium is through the gut. The greater excretion of calcium into the gut will account for the hypocalcemia which is described. I repeat again from the present point of view that hypocalcemia which has been described can be considered the effect of tetany rather than its cause. I am in thorough accord with Dr. Dragstedt's views.

Just one word as to the result of the injection of calcium compounds. Those who have used this method recognize the fact that animals fail to survive following intravenous injection of calcium compounds in spite of the fact that the early results were beneficial. The literature is full of protocols of animals that died in spite of the intravenous injection of calcium. We have an accurate explanation for these failures, that when calcium salts are injected they have a nephrolytic action. In one animal the intravenous injection of calcium salts produced an anuria and there was 17 per cent albumen. It has been shown that the injection of these compounds exerts a deleterious effect on the kidney parenchyma due to the fact that these toxins are so soluble. I can well understand why those who tried to keep such animals alive did not succeed. They overlooked the chief factor, the excretion of the kidney. As a result of that the animals died from tetany, not in spite of the intravenous injection of calcium, but because of it.

Dr. Walter M. Boothby, Rochester, Minn.: We have had at the Mayo Clinic in the past two years three cases of parathyroid tetany, and, of course, it has been incumbent upon us to keep them alive. This work of Dr. Dragstedt and Dr. Luckhardt is exceedingly impor-

tant. I will not enter into detail as to whether the cause is due to lack of calcium or whether it is due to toxemia. From the clinical point of view at the present time that is the least interesting, though of course it is a vital problem to work upon.

We have approximately 1500 thyroidectomies a year and we usually have out of that number one or two cases of parathyroid tetany; that is, it occurs in about 1 in 1500 or 1 in 1000 cases of thyroid operation that we perform. It is an accident that must be taken care of. This work that Dr. Dragstedt has reported, and also Dr. Luckhardt's, has helped us a great deal in keeping these patients alive. We have confined our attention mainly to keeping up the blood calcium. Clinically about four days or three days after operation the patient who is going to have parathyroid tetany will feel a twinge of the facial nerve. If that occurs twice we can be sure that the blood calcium is becoming decreased. Ordinarily the blood calcium will run about 10 mg. About the third day when the patient shows the first sign of tetany the blood calcium will be down to the region of 7. It is then necessary to start the calcium and keep the blood calcium up above 7, which seems to be the critical line, to prevent tetany.

The administration of calcium is a trick that has to be learned. In the first place, calcium lactate has to be dissolved in water. In the second place, it must be given in large doses and not too frequently. Sixty grains dissolved in water every three hours day and night are required at first, but as time proceeds there seems to be a readjustment. We have assumed that this is a readjustment of a non-organic substance. At all events, the individual will be able to run along very well with the blood calcium low, better than he did at first. For instance, after two or three months he will not go into tetany when the blood calcium drops down to 6 or 7. He seems to be able to stand that concentration much better than at first. He will, however, go into tetany again if the calcium is stopped, and also show a marked drop in the blood calcium line.

Intravenous calcium is not good: one cannot inject very much, and sloughing due to accidental introduction of the salt into the tissues about the puncture is likely to occur.

Surgeons, when they see a case of parathyroid tetany are likely to get alarmed and want to give an intravenous injection. This is a surgical procedure. Parathyroid tetany in the human being can be controlled in one-half hour by giving calcium lactate by mouth, if it is given in large doses. We let the patient develop actual tetany before we start the calcium, because there are a certain number of hysterical manifestations after thyroid operations that have a similarity to those of patients with low blood calcium. These patients are perfectly well taken care of by the ordinary routine treatment. If there are any cramps, if the fingers are drawn up, with fine twitchings, with the legs drawn up, if they are in severe pain, the thing to do is to give calcium lactate every 15 minutes until they are out of it, and then every two or three hours for two weeks. Then the dose can be decreased until the body has become adjusted to the lower calcium level.

Dr. W. F. Walter, Washington, D. C.: I am very much interested in the paper which Dr. Dragstedt has presented, and particularly interested in the fact that he removes the entire thyroid gland as well as the parathyroids. I should like to ask Dr. Dragstedt if in these animals that have died there has been a post-mortem examination, and what pathological conditions were found in the other endocrine glands; also, in the female dogs which have been operated on, if pregnancy has occurred in any of them. Perhaps I had better state it rather under my breath, but in patients suffering from exophthalmic goiter I was taught to leave two-fifths of the gland, and I did it

with many recurrences and more incomplete recoveries. Then I left only one-fifth, and then less and less, until I have removed from seven patients suffering from exophthalmic goiter the entire thyroid gland. These patients are still alive and they are not suffering from any hypothyroid symptoms or myxedema. I would like also to ask Dr. Dragstedt if these dogs showed any signs of myxedema.

Dr. J. P. O'Neil, Chicago: Two years ago I first heard of the work of Dr. Dragstedt and Dr. Luckhardt, and about the same time I had a case that came into this field. It was a woman who had a history of epilepsy at the age of 28. She had never been operated on for thyroid disease, though she had a large adenoma removed four or five years later. The first attack of epilepsy occurred at 17, the second at 28. They always came on following excitement. At about the age of 30 she began to have more attacks, and at about 35 they began to come on once a week or once every two weeks. The peculiar thing about the case was this: if the attack began on Friday she would run continuously on Friday and therefore the probability of hysteria had to be considered. She had consulted some of the best neurologists in Chicago, in the East and in the South, and the unanimous opinion was that it was a true epilepsy.

Following the idea of Dragstedt and Luckhardt—and a little before that—I had begun working on the basis that it was an endocrine disturbance. No previous treatment had been of any avail. It had not been possible at any time to get the feces absolutely odorless or colorless. Since beginning treatment she has had three separate attacks in two years, each one of which could be attributed to the fact that she had partaken of a diet high in protein and high in meat. She would know six or eight hours before that an attack was approaching. It usually followed a sleepless night. Many of them have been averted but she has had three.

Dr. Lester R. Dragstedt, Chicago (closing the discussion): Dr. Luckhardt and I worked from an entirely different angle. I would like to emphasize again that there is no real contradiction between the work on calcium, the relief of parathyroid tetany by the administration of calcium, and the experimental and clinical observations indicating that the condition is a toxemia. Much might be said with regard to this view of the pathogenesis of tetany in analyzing the various types of clinical tetany, tetany in children, in gastro-intestinal disorders, after infection, after toxemias, after intestinal obstruction, etc.

I was very much interested in the report by Dr. Boothby of the use of calcium in clinical parathyroid tetany. We have seen a number of such cases respond to calcium administration in the same way that our experimental animals responded. There is nothing to indicate that the clinical parathyroid tetany is any different from experimental parathyroid tetany.

With regard to the adjustment or compensation which occurs in animals or man after parathyroid extirpation we may report this experiment: If the animal has been controlled by any method following complete thyroidectomy for a period of six to eight weeks, he thereafter may remain in good condition without treatment. It is possible that some adjustment has taken place in some of the other organs so that they may have taken over the function of the missing glands. The administration of phosphorus to animals that have been relieved will throw them into violent tetany, the symptoms being the same as those following acute removal.

A number of parathyroidectomized animals have come to autopsy. Some of them died spontaneously and some were killed. These animals showed no definite pathologic lesions in any of the organs. We

have thought that there might be a slight enlargement of the adrenal glands but that cannot be stated with any degree of certainty.

A number of these animals that have been operated on and recovered have become pregnant. It is interesting that these animals which became pregnant following complete parathyroidectomy and had been normal for a month or so, during the latter part of pregnancy developed violent convulsions, much like those occurring in animals recently operated on, and there were many things in this condition which suggested the convulsions occurring in pregnancy with eclampsia. I would not, however, like to give the impression that it is possible to completely cure the animal after removal of the parathyroid glands. These animals, although they may survive for a long period apparently normal, are not normal animals. They will develop tetany convulsions in case of pregnancy or oestrus, which resembles menstruation in the woman. Dr. Luckhardt noted in a number of his animals that months after operation, though the animals seemed normal, they developed bilateral cataracts. My animals showed exactly the same condition. Cataracts will begin in three months or six months and will lead to complete opacity of the lens.

It is interesting that we have not seen in any of our animals symptoms of myxedema. There can be no question but that we removed all the thyroid tissue in the neck because we were not afraid to remove it. We tried to remove all the thyroid tissue and all the parathyroid tissue and we succeeded in perhaps 50 to 60 animals and kept them alive for a period of six months to two years. These animals did not develop myxedema. In many that were examined at autopsy we have not been able to find any trace of thyroid tissue in the chest. It may be that myxedema is a defect in metabolism which is manifested only in young animals. All the animals on which we operated were adults.

FURTHER OBSERVATIONS ON FEEDING INTERRENAL GLAND IN CASES OF GRAVES' DISEASE *

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In 1921 Marine and Baumann demonstrated that sublethal but sufficient destruction of the function of the interrenal glands in rabbits caused a sustained rise in heat production. Scott, working with cats, confirmed their results. The animals at autopsy showed thyroid hyperplasia and hypertrophy of the lymphoid tissues, particularly the thymus. From their results, these authors maintained that there exists an interrelation between the thyroid and the interrenal glands, the latter exerting an inhibitory or regulatory control over the thyroid. A functional interrenal insufficiency would consequently cause increased thyroid activity, its iodin store would become exhausted, which in turn would cause hyperplasia of the alveolar epithelium. From these and other experimental data they suggested that a functional interrenal insufficiency plays a fundamental role in the development of Graves' disease. Upon this basis we have been feeding ox interrenal glands to subjects of Graves' disease. On empiric grounds Solis-Cohen in 1896 and Crary in 1897 used desiccated preparations of suprarenal glands in the treatment of this condition.

In November, 1921, we published a clinical report of our first case so treated. This patient, in addition to other manifestations of improvement, showed rapid gain in weight (8.6 kg. first month and 10 kg. second month) and improvement in muscle strength following the oral administration of fresh ox interrenal glands. Since then we have studied the effects of feeding interrenal gland in a series of twenty cases of Graves' disease. The age groups of these patients were as follows: one was 9 years old; four were between 16 and 20 years; ten between 31 and 38; four between 40 and 48, and one was 62 years old.

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All except two were females. Two of the subjects had had x-ray treatments of the thyroid area before admission but without improvement.

The preparation used by us was a 50 per cent glycerol emulsion of fresh ox interrenal glands. This is made in the following manner: the glands are carefully freed of fat and then split sagittally; the medulla is carefully dissected out with scissors (if well done this removes approximately 90 per cent of the epinephrin containing tissue); the cortical portion is then hashed and mixed with equal parts by weight of glycerol. This preparation can be kept in the ice-box for two weeks without deteriorating. The average dose was 30 cc. daily. This preparation was readily taken as a rule by the patients without untoward symptoms.

The outstanding effects were a rapid gain in body weight and improvement in muscle strength. This gain in weight was most striking in the emaciated patients, and furthermore ceased when it reached approximately the normal weight of the patient before the onset of the disease. Associated with the improvement of muscle strength there occurred in the asthenic patients with hypotension a progressive rise in blood pressure to about the normal level, where it remained.

Concomitant with the increase in body weight there occurred a temporary rise in heat production. This increase in metabolism with relatively slight remissions was found to persist as long as three months after medication was stopped without any fall in weight. In an attempt to lower the heightened metabolic rate we subsequently exposed five of the patients to x-ray treatment. Three of these showed a drop to normal and have been active and well since. Of the other two, one has had a subtotal thyroidectomy performed and showed only a temporary postoperative drop, plus 40 to plus 20 per cent, followed by a rise to almost the previous level (plus 30 per cent). The other patient has been fairly active but still shows high metabolism (plus 39 per cent) in spite of the x-ray treatments.

Another effect, a source of great relief to the patient, was the influence upon abnormal menstruation which is a common accompaniment of Graves' disease. Seven of the women complained of severe dysmenorrhea. In each of these we observed

a very decided improvement in this distressing symptom. In one subject with prolonged bleeding time and who showed purpuric spots over the body and had menstrual hemorrhages so profuse as to necessitate on one previous occasion a blood transfusion, we observed an arrest of the hemorrhages with decrease in bleeding time from 8 to 4 minutes and disappearance of the purpura. On three different occasions this patient showed return of all these symptoms following cessation of the feedings, and each time we observed alleviation of the symptoms following the resumption of interrenal gland administration. In two other cases we likewise observed reappearance of the dysmenorrhea following discontinuance of the interrenal feedings and also subsequent disappearance of the symptoms after the feedings were resumed.

Diarrhea was a common symptom and usually disappeared at the same time that improvement in general condition occurred. One patient had severe chronic diarrhea, averaging about 20 bowel movements daily. This condition was gradually controlled following interrenal emulsion feedings. It reappeared following cessation of feedings and was again controlled on three different occasions since her discharge from the hospital following oral administration of ox interrenal emulsion.

Four cases illustrative of the group will be described briefly.

Case I: A housemaid, 16 years of age, complained of enlargement of the neck, increased nervousness and excessive perspiration, for about one month. Her appetite had been increasing since the onset of these symptoms. Menstruation commenced at 14, occurred every 28 days, lasted 4 days, and was regular and painless.

Status: She showed flushed face, questionable exophthalmos, symmetrically enlarged thyroid, fine tremor of fingers, and moist warm palms. The heart was not enlarged; there were no murmurs and the rate was 96. The blood pressure was 145-90; the weight, 56.8 kg. The basal metabolic rate was plus 24 per cent. The urine was negative for sugar and albumin. The blood count showed 36 per cent lymphocytes.

She received 30 cc. daily of a 50 per cent emulsion. Two weeks later her pulse was 78, blood pressure 130-80, and weight 57.7 kg. Her basal metabolism dropped to plus 3 per cent. We continued the feedings two weeks longer, or one month in all, after which she showed a further increase in weight to 59 kg.; the pulse remained about 70 per minute; the blood pressure was 120-80. The flushed appearance of her face was no longer observed. She seemed well, was working and active. She was seen at irregular intervals for the next four months. There was no reappearance of her symptoms. Her thyroid had decreased in size and was only slightly enlarged.

Case II: A girl, 19 years of age, bookkeeper, was admitted to Montefiore Hospital, March 7, 1922. During 1918, at the age of 15, the patient developed thyroid enlargement which receded following

the administration of iodin. She then started to menstruate. In 1920 her neck again enlarged, and at the same time she commenced to lose weight and to tire easily. She was given large doses of an iodin containing preparation following which she continued to lose weight more rapidly and to grow progressively weaker. She complained of palpitation, excessive perspiration and increased prominence of her eyes. Her menstruation gradually lessened in amount and become very painful. The month before admission there was amenorrhea.

Status: The patient was an emaciated young girl, extremely nervous, tossing about in bed, with choreaform movements and marked bilateral exophthalmos. She was bedridden and weighed 39 kg. The thyroid was large, symmetrical and very firm in consistency (iodin involution); thrill and bruit were present over it but there was no expansile pulsation. The heart was enlarged; the rate was 144 and there was a systolic murmur over the precordium. Marked throbbing of vessels of neck was observed. There was a fine tremor of the fingers, wasting of muscles and asthenia. The urine showed a trace of sugar. There was incontinence of urine and feces. Basal metabolic rate was plus 47 per cent; the blood pressure, 140-75.

The patient was kept in bed for two weeks. The pulse remained about 140; there was slight lessening of her nervousness. Basal metabolism was plus 46 per cent; the weight remained 39.0 kg. Following this, she took 30 cc. of glycerol emulsion of ox interrenal glands daily. Within two weeks there was slight increase in weight and a rise in metabolism to plus 70 per cent. After about one month her weight increased to 44.5 kg. and the metabolic rate was plus 58 per cent. After ten weeks of feeding with this emulsion she showed a total gain of 11 kg. Her basal metabolism was plus 52 per cent. There was no change in the pulse rate, which averaged 120 throughout. There was a marked improvement in muscle strength, so that the patient was able to climb a flight of stairs with little distress. At the same time that this improvement occurred the thyroid increased in size (from 36 cm. to 38 cm. neck circumference) and became softer in consistency. There was considerable new growth of scalp and axillary hair, very slight improvement in exophthalmos and disappearance of glycosuria. During the next month the patient showed no changes except a further increase in weight. X-ray treatments of the thyroid area were then started. She received four exposures in the next three months. There was a drop in metabolism to plus 31 per cent and return of menstruation. The patient returned to her home and resumed her work. She reported for observation seven months later, at which time her basal metabolism was minus 6 per cent; her weight, 59.1 kg.; her pulse, 84, and blood pressure, 115-85. The urine was negative for sugar and albumin. She was active and apparently well. Her exophthalmos was still definitely present. Menstruation was normal and regular. The thyroid was still definitely enlarged, soft in consistency, no bruit or thrill being present. We attempted to produce further reduction of the thyroid by administration of minute doses of desiccated thyroid and iodin. However, the patient was still sensitive to these and consequently the attempt was abandoned.

Case III: A housewife, married, 38 years of age, was admitted to Montefiore Hospital on April 5, 1922. Onset of her illness dated back to about a year and one-half previous to admission. The patient commenced to lose weight and to grow very weak. She had lost 55 pounds up to the time she entered the hospital. Menstruation had commenced at 14 years and occurred every 28 days, lasting 4 days. Since onset of the present illness it had become irregular and very

painful. Upon admission she had become so weak that she was scarcely able to stand.

Status: The subject showed an anxious expression and mild exophthalmos; the skin hung loosely, significant of loss of much weight, and was warm and moist. The thyroid was symmetrically enlarged and firm in consistency; loud bruit and thrill were present and throbbing of the neck vessels. The heart was enlarged; the rate was 130; there was loud systolic over the precordium, accentuated second aortic and very severe myasthenia out of proportion to all other symptoms. The blood pressure was 170-75; blood count showed 39 per cent lymphocytes. The urine contained a trace of sugar. Her weight was 66.3 kg., and basal metabolic rate was plus 70 per cent.

The patient was kept in bed and given full diet and mild sedatives. She remained in the hospital one month, during which time we attempted to feed her glycerol emulsion of ox interrenal, but owing to its fleshy odor the patient refused medication. We did not attempt to administer this again during her stay. There was loss in weight from 66.3 to 63.6 kg.; her basal metabolic rate remained between plus 70 and plus 74 per cent; her pulse remained between 105 and 130; the blood pressure dropped slightly to 160-90.

She then returned home, where she remained in bed owing to her weakness. She returned for observation on May 18, about a week after she left the hospital. The pulse was 106, the weight was 61.8 kg., and basal metabolism plus 68 per cent. On June 12 she developed auricular fibrillation and signs of cardiac decompensation, including cyanosis, dyspnoea and rales over the bases of both lungs. Digitalis was administered. After one week the acute cardiac upset was controlled. Her heart rate averaged 120, with an occasional extra systole. On this day we started administration of glycerol emulsion of ox interrenal glands, 45 cc. daily. This time she retained this preparation without any untoward symptoms. Within two weeks she was well enough to come to the hospital again for a basal metabolic rate determination. Her heart was regular, averaging 96 beats per minute, and the blood pressure was 145-85. Her weight increased to 66.3 kg. There was a sharp rise in metabolism to plus 103 per cent. We continued the administration of interrenal emulsion and also of digitalis. Three weeks later her pulse remained about 90 and was regular. She showed definite improvement in muscle strength so that she was able to carry on her housework to a limited degree. Her weight increased to 70.4 kg. Her metabolism had dropped to plus 79 per cent. She was seen again after an interval of three weeks. Her pulse rate remained unchanged. Her weight was 68.6 kg. and her basal metabolic rate was plus 68 per cent. We then discontinued the interrenal feedings and one month later started X-ray treatments, giving her four exposures during the next three months. Her metabolism showed only a slight drop, averaging plus 56 per cent. Her weight remained at 75 kg. Her pulse averaged about 96. In spite of her high metabolism she was active and fairly comfortable. Observation made 9 months later showed a drop in metabolism to plus 16 per cent and a gain in weight to 81.4 kg. Four months subsequent to that, however, her B. M. R. had risen to plus 55 per cent again. Her weight dropped to 72.3 kg. and she seemed worse as compared with the last observation. On May 15, 1924, she again reported to the hospital. Her weight was 82 kg.; pulse, 80; B. M. R., plus 39 per cent. She feels well, is active and does her housework. Her thyroid remains symmetrically enlarged. The bruit, however, is no longer heard. She is still somewhat nervous and excitable and still shows slight exophthalmos.

Case IV: A high school student, 19 years of age, was admitted to Montefiore Hospital on May 29, 1922. During the summer of 1919 she noticed that she tired very easily. She later complained of frequent palpitation of the heart and excessive perspiration and nervousness. Her weight was 59 kg. She rested most of the summer and there was slight improvement of symptoms. Subsequently she developed enlargement of the thyroid and exophthalmos. At the same time her weight had dropped to 50.4 kg. on admission. Menstruation commenced at 13, was irregular, painful, and since onset of the present illness, profuse.

Status: The nourishment was fair; the patient appeared excited and nervous. Moderate bilateral exophthalmos and large diseased tonsils were noted. There was a symmetrically enlarged thyroid, soft in consistency; thrill and bruit were present. There was throbbing of the neck vessels. The heart was not enlarged; the rate was 110 and regular; a faint systolic murmur was heard over the base. The blood pressure was 125-60. Tremor of the fingers was present; the palms were moist and warm. Muscle strength was fair. The basal metabolic rate was plus 30 per cent.

The patient was put to bed on full diet and mild sedatives for one week. After this time there was no change in weight; the pulse averaged 100 to 110. There was troublesome diarrhea since admission which did not abate during this period. She then received 30 cc. daily of glycerol emulsion of ox interrenal. During the following week there was a profuse painful menstruation. Her pulse averaged 96; blood pressure, 110-65; basal metabolic rate, plus 30 per cent; diarrhea gradually lessened. There was a gain in weight to 53.1 kg. After three weeks she showed a total gain of 4.1 kg. and a rise in metabolism to plus 39 per cent. Her pulse averaged 90; the blood pressure was 110-80, and diarrhea was controlled. Tonsillectomy was then performed under local anesthesia. She left the hospital on July 20. At that time her pulse averaged between 80 and 85. The blood pressure was 115-80; weight, 55.4 kg., and basal metabolic rate, plus 28 per cent. All subjective symptoms except occasional palpitation of heart abated. Exophthalmos which was mild receded. Menstruation was slightly painful but no longer profuse. Muscle strength was good. One month later she returned for observation. Since she left hospital she had remained at home, fairly active, feeling well, taking emulsion daily. Her weight was 55.9 kg., the pulse 95, and basal metabolic rate plus 31 per cent. The following menstruation was normal. At this time administration of interrenal emulsion was discontinued. The patient was given 5 X-ray treatments during the next four months, during which there was bradycardia of 54 beats per minute, increase in weight to 61.3 kg. and fall in basal metabolism to minus 18 per cent. One month later metabolism was plus 1 per cent; weight, 59.5 kg.; bradycardia persisted 54 beats per minute. Electrocardiagraph showed sino-auricular block, L. V. P., sinus, arrhythmia, and bradycardia. This condition has persisted to the present day. The patient is now a school teacher, active, and feels well. The pulse is still slightly irregular, menstruation is normal, and exophthalmos is no longer present. Thyroid gland is palpable and firm in consistency; no bruit or thrill present. The blood pressure is 120-80, and the basal metabolism is normal.

DISCUSSION

Marine and Lenhart in 1911 collected data showing that the conception that Graves' disease is a thyroid disease is untenable.

Their conclusion at that time was: "The essential physiological disturbance in the thyroid in exophthalmic goiter is a relative insufficiency, its reaction compensatory and its significance symptomatic." The facts that sufficient injury to interrenal function (as developed by Golyakowski, Marine and Baumann, and by Scott) leads to a chronic increase in heat production and that removal of the thyroid prevents it are undoubtedly of great importance as regards the etiology of exophthalmic goiter. We believe that this is the nearest approach to the experimental production of Graves' disease in animals that has yet been obtained. Indeed, the clinical manifestations of acute cases of Graves' disease are almost identical with the clinical manifestations produced in rabbits and cats by sufficient but sublethal suppression of interrenal function as shown in the following table:

INTERRENAL INSUFFICIENCY	GRAVES' DISEASE
(a) Increased B.M.R. (usually) Associated with increased appetite.	(a) Increased B.M.R. (usually) Associated with increased appetite
(b) Thyroid hyperplasia.	(b) Thyroid hyperplasia.
(c) Lymphoid hypertrophy	(c) Lymphoid hypertrophy
1. Thymic enlargement	1. Thymic enlargement
2. General lymphoid enlargement (hypertrophy)	2. General lymphoid enlargement (hypertrophy)
(d) Asthenia	(d) Asthenia
(e) Increased sexual activity	(e) Increased sexual activity (abnormal menstruation)
(f) Hypersensitiveness	(f) Hypersensitiveness
1. Toxins	1. Toxins (acute intercurrent infections)
2. Drugs	2. Drugs (epinephrin)
(g) Increased peristalsis	(g) Increased peristalsis

Marine and Baumann pointed out that this conception of exophthalmic goiter would explain the continued lymphoid and thyroid stimulation as in part dependent upon weakness or exhaustion of the interrenal glands associated with normal or increased functional activity of the chromaffin tissue. These authors are careful to state that while interrenal injury alone or combined with increased epinephrin discharge represents two of the essential alterations from which many of the disturbed interrelations directly or indirectly arise, they do not believe that they will fully explain exophthalmic goiter.

The principal clinical phenomena which we have observed to be beneficially affected following the oral administration of

glycerol emulsion of ox interrenal glands in cases of Graves' disease were as follows:

1. Asthenia.
2. Dysmenorrhea.
3. Diarrhea.
4. Body nutrition.
5. Heat production.
6. Tachycardia.
7. Blood pressure.

Asthenia is one of the most constant clinical manifestations of Graves' disease. It is an additional expression of the insufficiency shown by these patients in the transformation of energy into work, which has recently been emphasized by Boothby and Plummer. It is the most prominent clinical symptom of states in which, in our opinion, interrenal insufficiency plays a fundamental role, notably exophthalmic goiter, Addison's disease, status thymicolymphaticus and status thymicus, experimentally produced by bilateral suprarenalectomy. On the other hand, in contrast with this, let me emphasize that we observed striking improvement in asthenia and what we have interpreted as increased efficiency, both in storage and utilization of energy following feedings with interrenal gland emulsion. We believe that the interrenal gland contains a substance capable of restoring to the cell its capacity to perform such functions more efficiently. These effects have not been observed with the dried preparations that we have tried up to the present time, with the possible exception of acetone extracted glands. Furthermore, we believe that the effects observed are the manifestations of only infinitesimal traces that have escaped destruction in preparation and through digestion. These manifestations are, therefore, only glimpses of what may be realized when these substances are concentrated and prepared so that they may be introduced parenterally. This has been classically illustrated in the differences in their respective actions observed between oral and parenteral administration of other hormones such as epinephrin, insulin and the growth-producing principle of the anterior pituitary. In thousands of feeding experiments Uhlenhuth and others have obtained in a few instances glimpses of growth acceleration, whereas Evans has shown that this effect can invariably be pro-

duced in white rats by the intraperitoneal injections of a preparation of anterior pituitary.

The improvement that we have observed in disturbances accompanying menstruation, chiefly pain and excessive hemorrhage, also deserves emphasis. We believe that this influence upon ovarian activity is accomplished through the close functional relation that exists between the ovaries and the interrenal glands.

We have seen in ten instances a gradual fall in basal metabolism and pulse rate after a preliminary rise to within normal limits within 3 to 4 months after the interrenal feedings were stopped. In three of these cases x-ray treatments of the thyroid area were given during that interval. However, in two other instances the patients had received without relief Roentgen ray treatment of the thyroid area before administration and showed definite improvement after interrenal feedings. It is our impression that those three subjects showing the decrease in metabolism and pulse rate after x-ray treatment were destined to show these changes anyway, but that they may have been accelerated by the x-ray exposures. Some of our patients have shown decrease in heat production following the oral administration of interrenal emulsion and without any x-ray treatments.

In conclusion I wish to point out that evidence is rapidly accumulating that the interrenal glands exert an inhibitory or regulatory control over the thyroid and that a functional interrenal insufficiency plays a fundamental role in the development of Graves' disease. In a series of twenty cases we have uniformly observed beneficial effects, notably rapid increase in body weight and concomitant improvement in muscle strength following the oral administration of glycerol emulsion of ox interrenal glands.

CASE I.

Date	*Pulse*	*Weight*	*B.M.R.*	*Remarks*
1-5-22	96	56.8 Kg.	+24%	Started Interrenal Emulsion
1-19	78	57.7 Kg.	+ 3%	
1-31	80	59.0 Kg.	— 2%	Stopped Interrenal Emulsion
2-28	76	59.0 Kg.	— 6%	
3-30	70	59.0 Kg.	— 6%	
6-22	74	59.0 Kg.	— 1%	

CASE II.

Date	*Pulse*	*Weight*	*B.M.R.*	*Remarks*
3-9-22	144	39.0 Kg.	+47%	
3-14	136	39.0 Kg.	+46%	Started Interrenal Feedings
3-21	124	38.1 Kg.	+62%	
3-28	120	39.5 Kg.	+70%	
4-11	120	40.0 Kg.	+63%	
4-27	124	44.5 Kg.	+58%	
5-9	120	48.1 Kg.	+58%	
5-16	114	47.9 Kg.	+45%	
5-23	124	49.3 Kg.	+52%	
5-31	130	50.0 Kg.	+54%	X-ray treatment, 6-24, 7-8
7-13	114	53.1 Kg.	+39%	Stopped Interrenal Feedings
8-15	110	53.4 Kg.	+42%	X-ray treatment, 7-24, 8-24
11-9	108	53.1 Kg.	+31%	X-ray treatment, 11-21
7-26-23	84	59.0 Kg.	— 6%	
11-3	80	60.5 Kg.		

CASE III.

Date	*Pulse*	*Weight*	*B.M.R.*	*Remarks*
4-18-22	130	66.3 Kg.	+70%	
4-27	105	65.4 Kg.	+76%	
5-9	120	63.6 Kg.	+74%	
5-18	106	61.8 Kg.	+68%	Started Interrenal Feedings
6-29	96	66.3 Kg.	+103%	6-19
7-18	90	70.4 Kg.	+79%	
8-8	90	68.6 Kg.	+68%	Stopped Interrenal Feedings
10-31	96	70.0 Kg.	+62%	X-ray treatment, 9-11, 10-5
12-14	96	75.0 Kg.	+56%	10-26, 11-23
9-13-23	89	81.4 Kg.	+16%	
1-29-24	108	72.3 Kg.	+55%	
5-15-24	80	82.0 Kg.	+39%	

CASE IV.

Date	*Pulse*	*Weight*	*B.M.R.*	*Remarks*
6-6-22	110	50.4 Kg.	+30%	Started Interrenal Feedings
6-13	96	53.1 Kg.	+30%	
6-27	90	54.5 Kg.	+39%	
7-18	84	55.4 Kg.	+28%	X-ray treatment, 7-22, 8-14
8-17	95	55.9 Kg.	+31%	X-ray treatment, 9-11, 10-10 11-18

9-30	90	56.8 Kg.		Stopped Interrenal Feedings
11-7	54	60.9 Kg.	—16%	
11-16	42	61.3 Kg.	—18%	
12-17	54	59.5 Kg.	+ 1%	
1-19-23	54	59.0 Kg.	+ 1%	
10-13	54	54.0 Kg.	— 3%	
1-4-24	60	55.0 Kg.		
4-26	54	55.0 Kg.		

DISCUSSION OF PAPER OF DR. SHAPIRO

Dr. Walter Timme, New York: I would like to ask Dr. Shapiro how the emulsion of the cortex is prepared and where the extract is obtained.

Dr. Shapiro, New York City: By an arrangement that we have with the veterinarians in a slaughter house in New York City, we are able to obtain the glands immediately after their removal from the oxen. The method of preparation consists of carefully freeing the glands of fat and then splitting them sagittally. The medulla is carefully dissected out and the remaining cortical portion is then hashed and emulsfied with glycerol.

Editorial

BIBLIOGRAPHIES

To one who is not conversant with the routine of an editorial office it would perhaps come as a surprise to learn how much unedifying labor is required to insure satisfactory bibliographic work. Taken by and large, even with much expenditure of time upon the part of editors, satisfactory results are by no means always achieved. In case of books, no little slip-shod work is tolerated by even excellent publishing houses. Some of the difficulties have been admirably expressed by the Editor of the *Journal of Radiology* in the May, 1924, issue (page 168).

"An editorial writer in a recent medical publication notes with pained surprise," it is stated, "what has long been an annoying and glaring fault in the great majority of American medical writers, namely, such a lack of accuracy in bibliographies as to render them a source of much wrath to anyone attempting to look up the literature to which they refer. It is rare to find that a bibliography has been carefully and accurately checked by the author or by some one else competent to do it. Frequently the author jots down his references inaccurately; sometimes it is even worse than this, and he exhibits a total lack of knowledge as to what a complete citation should include.

"Recently the writer witnessed an author checking a bibliography appended to the manuscript of a really worth-while book which he was about to have published. The bibliography was long, the author was weary with an unaccustomed and uninteresting task, a task much lightened for him, however, by the services (free gratis) of an excellent medical librarian. Several times the librarian remarked of a book, 'Edition so and so,' or of an author's name, 'Initials so and so,' only to be met with the reply, 'Oh, that does not matter.' In citing the page, volume, month and year of a reference to a periodical she was told sev-

eral times that the learned doctor cared not at all for one or the other of these items, he seemed quite satisfied if he had either the volume or the year. It never entered his head that many times, through some slip of the stenographer or the proof-reader, the volume number becomes most useful as a check upon the year, and vice versa, nor that the page number might save the reader's looking through the index of the volume referred to and thus save some busy doctor's time, to say nothing of his patience.

"Such carelessness is inexcusable, but it is often met. Only the librarian and the man who does his own literary research has any idea of the waste of time and the annoyance so caused. Anywhere from five minutes to half a day may be required to run down a reference. True, it is not often that the reference is needed badly enough to spend a half day searching for it, but sometimes it is. Another editorial writer recounts just such an experience. In looking up a certain bibliographic reference he traced it through five articles before he found the article to which the bibliography referred, for it was not original with B, to whom A's bibliography referred, nor yet with C, to whom B referred, nor to D, to whom C referred, nor yet with E, but its father was finally discovered in the person of F. Rather an extreme instance, but not a medical librarian in the country who does not have such an experience time and time again.

"As the writer first referred to says: 'It is an imposition upon readers to present to them a list of references to the literature of a subject, only to have them discover after an annoying search that many of the references are incorrect, that some of the articles cannot be found, and that others have no bearing upon the subject.'

"Such slovenliness is a reflection upon American scholarship and often dims its brilliancy in the eyes of our more careful colleagues across the seas."

A besetting sin of Americans is rushing madly toward some goal, often with little probability that the goal is worth the strain. It is not fair, however, that in such strenuosity writers should carelessly add to the existing confusion in the medical literature.—R. G. H.

Book Reviews

LECTURES ON ENDOCRINOLOGY. Walter Timme, Paul B. Hoeber, Inc., New York, 1924. Pp. 123, 8°.

This little book is frankly a verbatim reprint of an article published by the author in the periodical literature in 1921. As such it, of course, takes no cognizance of much interesting work that has appeared since that date, and its restricted size precludes detailed consideration of most of the earlier work. One gathers the impression that the lectures are of interest primarily as setting forth the working theories of an alert clinician confronted with a somewhat bewildering array of constitutional anomalies with which he feels constrained to attempt to deal helpfully. The book is written in a delightfully entertaining style.—R. G. H.

THE HUMAN TESTIS AND ITS DISEASES. Max Thorek. J. B. Lippincott Co., Philadelphia and London, 1924. Pp. 548, 8°.

In this comprehensive work the author has brought together for the first time in a single volume in the English language a large proportion of the available data on the anatomy, physiology, pathology, diseases and therapeutics of the testis. Much emphasis is laid on the endocrine aspects of these topics. In addition to summaries of the work of others the author has incorporated the results of several years of personal study on the experimental and clinical phases of the subject. The book is well illustrated and is attractively printed.

In general, the literature has been judicially treated, though, as is inevitable in such a work, readers will differ as regards evaluation of specific contributions. The more conservative readers will regret the statement that "the endocrine doctrine teaches that character and mentality are not merely influenced by, but are the accurate and actual expressions of our secretions." This is an example of the sort of facile hokum from which the author has mostly steered clear.

The work would have been somewhat improved by more careful attention to elementary grammar and spelling. Sequence of tenses is not infrequently ignored; in a single line on page 179 "arthropods" and "tritons" are misspelled. Such defects are, however, not numerous. The author occasionally lapses into undue exuberance of style, as on page 75. The most serious criticism of the work is that the bibliographic material is left

in a deplorably shipshod form: the citations are lacking in uniformity and the references are often incomplete. Altogether, however, the book is one that will be welcomed by endocrinologists the world over. It will be found both instructive and entertaining.—R. G. H.

THE PARATHYROID GLANDS IN RELATION TO DISEASE. H. W. C. Vines, London: Arnold, 1924. Pp. 118. Figures 10. Price 10s 6d.

Reviewed in Physiol. Abst., 1924, **9**, 148.

Abstract Department

Increase of adrenin action by amino-acids (Weiterer Beitrag zur Kenntnis der Wirkungssteigerung von Adrenalin durch Aminosäuren). Abderhalden (E.) & Gellhorn (E.), Arch. f. d. ges. Physiol. (Berl.), 1924, **203**, 42-56.

Amino-acids so increase the action of adrenin on heart-strips that the minimal effective concentration is reduced to one-tenth. The effect is produced by d- and l-alanine, d- and l-leucine, d- and l-tyrosine, 3.5-di-iodo-tyrosine, l-histidine, and l-cystine, and also by beta-alanine. It is so far specific that amino-acids do not affect the action of other positive inotropic active agents as calcium and strontium chlorides. The lowering of temperature following intraperitoneal injection of adrenin into white mice is increased by addition of amino-acids.—A. T. C.

Castration and adrenals (Kastration und Nebennieren). Altenburger (H.), Arch. f. d. ges. Physiol. (Berl.), 1924, **202**, 668-669.

White mice, castrated at 3 weeks, showed three months later enlargement of the adrenal cortex and diminution of the medulla. The widening of the cortex equally involves the three zones.

—A. T. C.

The action of adrenalin on human digestion (L'azione dell' adrenalina sulla digestione gastrica dell' uomo). Bindi (N.), Gazz. d. osp. (Milano), 1922, **43**, 197-199.

Berti and Biavedoni's method is used. With 1 mg. of adrenalin Bindi observed some acceleration of functions. He therefore believes it to be a strong stimulant of the splanchnics which are said to determine the more active motor functions.—P. M. N.

Genito suprarenal syndrome (suprarenal virilism) in a girl one and a half years old, with successful operation. Collett (A.), Am. J. Dis. Child. (Chgo.), 1924, **27**, 204-218.

Family and personal history were normal until 9 months of age, when the patient had whooping cough. Abnormal growth of hair developed prior to this. Two months later she had an attack of bronchitis and convulsions. The child became plump, heavy, with rather a large head and general physical overgrowth; the vocal cords were unusually long and broad. Mentally she was quicker and cleverer than children of corresponding age. There was marked growth of hair on labia majora and mons veneris, on thighs, shoul-

der and back; there was no axillary hair. The genitals showed a well developed labia majora and mons veneris with a penis-like organ in place of the clitoris; hymen and uterus were normal. A tumor was felt on the left side under the costal margin. This was operated on and found to be a typical hypernephroma of rather long standing. Because of the infiltration with lime, the author considers that it was of early origin. When seen a year later, the child was more child-like in her appearance; all abnormal growth of hair had disappeared; there was less fat on the body and the genitals had somewhat receded in size. The author claims that this is the first case to be reported of a child who had survived removal of a tumor for a genito-suprarenal syndrome.—M. B. G.

A quantitative color reaction given by adrenalin and urine. Friend (H.), J. Biol. Chem. (Balt.), 1923, **57**, 497-505.

The color reaction given by pure solutions of adrenalin with sulfanilic and nitrous acids is quantitatively proportional to the adrenalin concentration. The reaction is no longer given after the adrenalin has been treated with ferric chloride. None of the urinary constituents tested has given a positive reaction before ferric chloride and a negative reaction after it. It appears possible that the urinary constituent giving the color reaction before, but not after the ferric chloride treatment, is adrenalin. Values for urinary adrenalin determined according to the method outlined in the paper are given for a number of pathological cases, including several of diabetes.—F. S. H.

Carbon dioxide and adrenaline as regulating factors for the musculature of the bronchi and pulmonary vessels. Magnus (R.), Brit. Ass. Adv. Sc. Rep., 1923, 478-479.

Experiments on surviving perfused cat lungs show that the bronchio-spasm produced by defibrinated or hirundinized blood is relaxed by the addition of 1.4-30% carbon dioxide to the air respired. Carbon dioxide in concentrations from 1.4% up causes in most cases constriction of the lung vessels, but when adrenalin is present in the blood in amounts over 1 part in a billion the effect of carbon dioxide is to cause dilatation. Changes in the concentration of O and N in the blood have no influence on the bronchial or vascular tone. It is concluded that carbon dioxide in physiological concentrations tends to maintain the air passage normal and in the presence of physiological amounts of adrenalin to facilitate pulmonary circulation. An increased alveolar carbon dioxide tension may, under pathological conditions, also have an important regulating influence.—Chem Abst., **18**, 1522.

Clinical studies in Addison's disease. Rowntree (L. G.), Tr. Ass. Am. Physicians, 1924, Atlantic City, May 6 & 7.

In the last 4 years we have had 21 cases of Addison's disease. Four patients received no treatment and died within a month; 5 received some form of organotherapy; 12 received full treatment and died despite the treatment; 5 showed very good results. Two recent cases cannot be fully reported on. We do not feel that influenza can be excluded from casual relationship. There was tuberculosis in 8 cases. Syphillis, malaria, typhoid fever, trauma and pregnancy, also played a part. Renal function showed very slow excretion of water. The blood plasma fell within normal limits. The blood does not flow readily. Lymphocytosis was a common occurrence. Liver function seemed to be normal. The basal metabolism was studied in 13 cases, and 8 were within normal limits; 4 were below normal. The breathing was very slow, with heavy sighing. The patient complained of cramps after taking suprarenal preparations, so the most recent method is to give preparations of the suprarenal cortex, which does not cause cramps to any extent. Pigmentation is usually increased in patients who do not improve under treatment. The treatment can combat functional insufficiency only of the suprarenal glands, but the treatment probably exerts no influence on the fundamental underlying factors; but results warrant giving the method a fair trial. The results of treatment depend on the patient's tolerance. In some instances an actual intolerance exists. In the shocklike crises we have given shock treatment first. Some patients can take 5 minims, some can take 20; the hypodermic administration causes less cramps than the oral method.—J. Am. M. Ass., **82**, 1886.

Suprarenal virilism. Scabell (A.), Deutsche Ztschr. f. Chir. (Leipz.), 1924, **185**, 1-46.

Scabell compares with 2 cases he describes 23 from the literature in which **pseudohermaphrodism** was associated with hyperplasia of the suprarenals, and 47 cases of precocious puberty, or virilism with acquired suprarenal hyperplasia. Hypoplasia of the bone marrow was a frequent finding, and was conspicuous in his 2 personal cases. In the first, the girl had been normal to the age of 12, when virilism developed, with a suprarenal tumor, which proved fatal in 3 years. In the other case hyperplasia of the suprarenals was associated with false female hermaphrodism. Scabell discusses suprarenal hypergenitalism in the congenital, acquired and rudimentary forms, with special regard to pathologic constitutions.—J. Am. M. Ass., **82**, 2092.

Experimental observations on the adrenals and the chromaffin system. Wislocki (G. B.) & Crowe (S. J.), Johns Hopkins Hosp. Bull. (Balt.), 1924, **35**, 187-193.

Adrenal insufficiency was produced in dogs by the combined surgical removal of a part of the adrenal glands and implantation

of radium in the remainder. The radium produced an area of necrosis which gradually destroyed the adrenal tissue. The medulla of the adrenals and the abdominal chromaffin body were destroyed in the dog without producing symptoms. A fragment of cortex amounting to about one-fifth of the total cortex was found to be necessary for the maintenance of life. After removal of all the cortex, the animals died with a terminal fall in blood pressure and temperature. If the cortex as well as the chromaffin system produces epinephrine, this fact would not explain the death of animals after extirpation of the cortex.—R. G. H.

The function of the carotid gland (Uber die Function der Carotisdrüse). Fischer (W.), Ztschr. f. d. ges. exper. Med. (Berl.), 1924, **39**, 477-486.

Investigations on kittens. Extirpation of the carotid bifurcation, together with the whole of the sessile gland on both sides (in a period of 6 to 20 days with 2 operations). As controls, kittens from the same litter were used. The consequences of the extirpation do not appear until after about 6 weeks, beginning with reduced liveliness, diminished appetite and playfulness, diffuse alopecia, inactivity of the extremities, backwardness in growth, retarded dentition, protruding abdomen, cachexia, spleen atrophy; the bones are porous, rough, having little calcareous content. The synchondrosis of the bones is widened by irregular zones of petrifaction. The suprarenal glands and epithelial bodies show a characteristic hypertrophy. The carotid gland has, apart from the function of the chromaphile system, functions which are of importance to growth and development of bone.—Physiol. Abst., **9**, 183.

Paget's disease and hyperspasmodic paraplegia in flexion (Maladie osseuse de Paget et paraplégie hyperspasmodique en flexion). Ardin-Delteil, Azoulay (R.) & Lagrot, Bull. et mém. Soc. med. d. hosp. d. Par., 1923, **47**, 920-924.

No definite syndrome of glandular or polyglandular disturbance was found in this case of Paget's disease. The injection of 2 mg. of **adrenaline** produced no noticeable reaction. The injection of 0.05 of hypophysis extract raised the blood pressure in 20 minutes from 19-10 to 20-11.—F. S. H.

Insulin-like substances (Ueber insulinartige Körper. I.). Brugsch (T.) & Horsters (H.), Biochem. Ztschr. (Berl.), 1924, **147**, 150-162.

Extract of **thyroid** gland in one case caused a slight lowering of the blood sugar in the rabbit. In two other instances it was ineffective. A slight depressant action of **parathyroid** extracts is reported. Extract of the **adrenals** gave the characteristic rise. **Liver** extract was followed by a rise in blood sugar. When a watery solution of an alcoholic extract of **spleen** was administered there oc-

curred a fall in blood sugar which persisted for some time. **Placenta** extract acted similarly and was found to be quite toxic to rabbits. Yeast, salts of phosphoric acids and arsenic acids caused lowering of blood sugar. An extract of **pancreas** was ineffective. Insulin seemed to stimulate bile secretion.—F. S. H.

Endocrine dysfunction as a possible etiologic factor in progressive deafness. Drury (D. W.), Boston M. & S. J., 1924, **190**, 1029-1033.

The author points to the **ovary, pituitary** and **thyroid** as glands possibly having an influence in progressive deafness. He bases this suggestion on the observation that in the 44 subjects he studied, 25 showed evidence of endocrine disturbances.—J. C. D.

Obesity. Faber (E. E.), Ugesk. f. Laeger (Copenhagen), 1923, **85**, 105-109 (Feb. 15).

Faber explains how the physiologic balance requires that the calory content of the food must equal the basal metabolism plus the work of digestion, plus the amount of energy used up in muscular work. He expresses this in the equation $C = B + D + M$. War experiences and research since have confirmed the view that the intake of calories is often above the physiologic requirement, and the superfluous calories throw an extra task on the organs which regulate oxidation and radiation of heat. If they are unequal to this task, the superfluous nourishment is deposited as fat. The metabolic anomaly in this endogenous obesity may not affect the basal metabolism, but **thyroid** treatment may stimulate the organs involved and lead to the throwing off of the fat deposits. Another point he emphasizes is that the organs involved (endocrine glands) may become exhausted from their extra work, so that even when the intake of calories is reduced very low they still are unable to cope with them. Obesity is rare in the young because their endocrine glands are so active that they can handle excess of work. In exophthalmic goiter the abnormally active thyroid diverts the energy to tremor and sweating rather than to accumulation of fat. The tendency to accumulation of fat increases as the endocrine system grows less active with advancing years. This is especially manifest in women at the menopause although the basal metabolism is normal. He remarks in conclusion that even the most pronounced cases of endogenous adiposity may show no benefit from thyroid or other treatment until the intake of food is materially reduced. This confirms the almost invariable blending of the endogenous and exogenous types.—J. Am. M. Ass., **80**, 1496.

Practical notes on endocrine therapy (Note pratiche di terapia endocrina). Fubini (E.), Rassegna di clin., terap. [etc.] (Roma), 1924, **23**, 61-73.

According to the author, glycerin extracts are preferable to dry preparations, and in pluriglandular disturbances each glandular substance should be administered separately in order not to destroy any of the incretory activities. Anaphylactic syndromes, hemoclastic autogenous crises, adrenal insufficiency and cases of osteomalacia have been successfully treated.—P. M. N.

The influence of the ovary and the thyroid on the regeneration of white and red blood cells (Beiträge zur Physiologie der Drüsen. L. Asher. Experimentelle Untersuchungen über den Einfluss der Drüsen mit innerer Sekretion auf die Wachstumsvorgänge, zugleich Beiträge zum Konstitutions-problem. I.) Furuya (K.), Biochem. Ztschr. (Berl.), 1924, **147**, 390-409.

Moderate loss of blood from thyroidectomized rabbits causes a slowing of the regeneration of the blood elements which is greater than that in ovariectomized animals. Moderate hemorrhage produces a definite increase in the polymorphonuclear count of normal rabbits and a relative decrease in the leucocytes. This alteration is less in degree in animals from which the ovaries have been removed and is lacking in thyroidectomized rabbits. These responses are taken as evidence for the belief that the ovary and thyroid exert an influence on the growth processes of the blood tissue and a similar though quantitatively different effect on bone marrow.—F. S. H.

The dependence of phagocytosis on internal secretion. A new method for the study of internal secretions. (Beiträge zur Physiologie der Drüsen. L. Asher. Experimentelle Untersuchungen über den Einfluss der Drüsen mit innerer Sekretion auf die Wachstumsvorgänge, zugleich Beiträge zum Konstitutions-problem. II.) Furuya (K.), Biochem. Ztschr. (Berl.), 1924, **147**, 410-424.

Hamburger's method for the study of phagocytic activity was used. It was found that the removal of the ovaries reduced the phagocytic activity of leucocytes toward carbon particles. Thyroid removal acted similarly but to a greater degree. The serum of thyroidless rabbits reduced the phagocytic power of normal exudate cells. The serum of ovariectomized animals had a like but lesser action. The phagocytic activity of cells from ovariectomized rabbits was also reduced by serum from thyroidless animals. Feeding thyroid substance to thyroidless animals raised the phagocytic power of the leucocytes to practically normal values. The same is true of feeding with ovary.—F. S. H.

Endocrinology from physician's point of view. Gow (A. E.), Brit. M. J. (Lond.), 1924, **i**. 697-700.

Gow is of the opinion that the majority of extracts of ductless glands, as at present prepared, have no obvious effect administered by mouth. Animal experiment has shown that tissue extracts in

general, when injected intravenously, have much the same effect as any other foreign protein, and, with few exceptions, are in no way specific. There is no evidence that any extract other than **thyroid** or **parathyroid** is absorbed as such from the alimentary tract. However, **epinephrin** is valuable in shock, in asthma and other spasmodic affections such as cardiospasm, urticaria and angioneurotic edema, and **pituitary** extract is a stimulant to a failing myocardium, especially in toxic myocarditis and in the third stage of labor. Gow states emphatically that if any advance in therapeutics is to be made with glandular extracts of doubtful action the practice of giving multiple extracts as a sort of blunderbuss, in the hope that one among the many may hit the mark, must be checked.—J. Am. M. Ass., **82**, 1895.

Influence of abnormal external temperatures on thyroids and testes (Beiträge zur biologischen Bedeutung der innersekretorischen Organe. II. Der Einfluss abnormer Aussentemperaturen auf Schilddrüse und Hoden), Hart (C.), Arch. f. d. ges. Physiol. (Berl.), 1922, **196**, 151-176.

House-mice, kept at 32°-40° C. for some days showed marked atrophy of the thyroid, with disappearance (sometimes almost complete) of colloid, marked degeneration of the spermatozoa-forming epithelium and complete cessation of spermatozoa production in the testes. When they were kept at 4°-7° C. there was increased thyroid function, colloid-packed follicles, and marked secretion-vacuoles in the cuboidal epithelium, while active spermatogenesis was visible in sections of the testes.—A. T. C.

A preliminary note on the properties of an alleged erythropoietic hormone. Leake (C. D.) & Bacon (F. J.), J. Pharmacol. & Exper. Therap. (Balt.), 1924, **23**, 353-363.

Desiccated spleen and red bone marrow combined in equal proportions by weight contain, on the average, 2.4 mgm. of water-soluble iron per gram, and 28.9 mgm. of lecithin-phosphatids per gram. Unless these substances represent integral components of the physiologically active agents in desiccated spleen and marrow, it is doubtful whether they can be considered much of a factor in the erythropoietic effects observed after the administration of spleen-marrow compound. In spleen and red bone marrow, erythropoietic agents are found which (a) withstand desiccation; (b) are thermostable at 100° Centigrade; (c) are water-soluble; (d) are inactivated by alcohol and ether; (e) are capable of oral administration; (f) are capable of biological assay; (g) do not deteriorate on standing in sterile solution, and (h) have no untoward accessory actions.
—R. G. H.

The purins of the blood and the influence of the incretory glands (Le purine del sangue e l'influenza su di esse delle glandole a

secrezione interna). Lovaglio (R.), Folia med. (Napoli), 1924, **10**, 296-306.

Splenectomy increases and **thyroidectomy** diminishes blood purins. Extirpation of the **parathyroids** probably is more important in this connection than that of the thyroid. The **adrenals** and **gonads** have but little influence.—P. M. N.

Changes in blood sugar (Ueber die Veränderungen des Blutzuckers. I.). Nakahayshi (S.) & Abelin (J.), Biochem. Ztschr. (Berl.), 1924, **147**, 544-556.

Studies on sheep and rabbits showed that a diminution of glycogen in the liver and hyperglycemia are not always accompanied by an increased sugar utilization. When **thyroid** is fed, the liver becomes almost glycogen free, but no increase in the respiratory quotient obtains. Also after **adrenalin** injection, in spite of glycogen mobilization and hyperglycemia and increase in gaseous exchange, there is only an insignificant increase in sugar oxidation. It was found that thyroid feeding induces no alteration in the behavior of the blood sugar. Before and after thyroid ingestion, as usual, the polarimeter value of the blood is less than that of the reduction value. The polarization value increases with time. After adrenalin injection there does occur a change in the blood sugar in that the polarization value becomes greater than the reducing value. It decreases on standing.—F. S. H.

Investigation concerning the influence of thyroid and ovarian treatment upon the development and the appearance of the feathers in birds (ducks) [Recherches concernant l'influence du traitement thyroïdien et ovarien sur le développement et l'aspect du plumage chez les Oiseaux (Canards)]. Parhon (C. I.) & Parhon (C.), Compt. rend. Soc. de biol. (Par.), 1923, **89**, 683-686.

Feeding thyroid to ducks 4 to 5 days old results in a retardation of growth and a delay in the growth of plumage. Feeding ovary had no appreciable effect.—T. C. B.

Chemical therapeutic agents and opotherapy (Les agents thérapeutiques chimiques et l'opothérapie). Pierrett (R.), Bull. gén. de thérap. [etc.] (Par.), 1924, **175**, 114-126.

Review.—F. S. H.

Internal secretion and gaseous exchange of blood. Yamakita (M.), Tohoku J. Exper. Med. (Sendai), 1922, **3**, 567-607.

The O loss of normal non-nucleated red corpuscles stored in the ice chest at 4° to 7° ranges from 50 to 80 per cent in 70 to 80 hours, but if mixed with **adrenaline** the O loss ranges from 15 to 40 per cent in the same time. If stored in the incubator at 34° to 38° the loss of O is 80 to 100 per cent in 15 to 50 hours, but in the

presence of adrenaline the decrease is 50 to 60 per cent. Generally the influence of adrenaline on carbon dioxid production is greater than on O consumption. In blood with or without adrenaline, O consumption and carbon dioxid production do not run closely parallel to each other; even after the entire loss of O the production of carbon dioxid can continue. Adrenaline has no influence on the O capacity of the blood. When the blood is hemolyzed the time taken for complete reduction is shortened, and by storage in the incubator for 10 hours the O is entirely lost, while if adrenaline is added the reduction of blood is retarded and is nearly the same as that for non-hemolyzed normal blood. Adrenaline has no relation to the serum, cell membrane, cell structure or stroma of the red corpuscles. The inhibitory action of adrenaline solution on the gaseous metabolism of blood is not due to chloretone contained in it, nor is it due to its acidity. HCl of the same acidity increases the rate of reduction of blood. Adrenaline also retards the rate of reduction of blood when it is treated with reducing gas. When the blood is reduced with carbon dioxid gas the effect is more marked than when nitrogen gas is used. Adrenaline does not accelerate the rate of oxidation but has a tendency to retard it. For a few minutes after the intravenous injection of adrenaline, just during the rise of the blood pressure, the blood of the external jugular vein is red-colored and contains nearly as much O as arterial blood. This action of adrenaline has no relation to the state of the blood flow. If blood is taken, within a few minutes after the intravenous injection of adrenaline, the gaseous exchange in vitro is much decreased. By the direct inhibitory action of adrenaline on the reduction of oxyhemoglobin the O supply to tissues and organs is disturbed, and there may occur anoxemia, which is further increased by constriction of the blood vessels. The inhibitory effect of adrenaline on the gaseous exchange of blood has no relation to white corpuscles, blood platelets or fibrin. Adrenaline and asphyxia produce many similar effects and phenomena in the body; some of the phenomena are explained by the anoxemia provoked by it. **Pituitrin** and **thyroprotein** have no similar effect on the gaseous metabolism in vivo or in vitro.—Chem. Abst., **17**, 2152.

Ovigenesis during sexual maturity. Allen (E.), Am. J. Anat. (Phila.), 1923, **31**, 439-481.

Carefully wrought line of evidence based upon experiments in white mice. The concept that the ova are differentiated in the ovary shortly after birth, or at least before the attainment of puberty, requiring that they remain dormant for long periods, is questioned. Allen holds that a cyclic proliferation of the germinal epithelium gives rise to a new addition of young ova to the cortex of the adult ovary at each normal oestrous period. An average of from 400 to 500 young ova may differentiate in one ovary at each period, while an average of 4½ ova of an earlier generation mature. The per-

centage of survival approximates only 1%. It is suggested that the periodical recurrence of ovigenesis during sexual maturity probably depends upon the maturation of a set of follicles from a preceding generation. The establishment of ovigenesis during sexual maturity makes this process more analogous to spermatogenesis.—W. J. A.

The origin of interstitial cells in the testis of the domestic cock (Sur l'origine des cellules interstitielles dans le testicule du Coq domestique). Benoit (J.), Compt. rend. Acad. d. sc. (Par.), 1923, **177**, 412-414.

These interstitial cells are formed during the second half of incubation and some days following hatching from the small epithelial cells of the sex cord. The latter become charged with fat, and migrate into the connective tisue. It is not possible to state definitely that the mesenchymatous cells take no part in the formation of the interstitial cells, but the probability is that they are formed solely from the small epithelial cells, not by degeneration but by a true metaplasia.—A. T. C.

Recent publications on sex (Quelques travaux récents relatifs aux problèmes de la sexualité). Coutière (H.), Biol. méd. (Par.), 1923, **21**, 193-234.

A general and complete review.—J. K.

Sex reversal in frogs and toads. A review of the recorded cases of abnormality of the reproductive system and an account of the breeding experiment. Crew (F. A. E.), J. Genetics (Cambridge, Eng.), 1921, **11**, 141-181.

In 40 subjects (32 Rana, 6 Bufo, 1 Pelobates, 1 Hyla) all degrees of primary sex intergradation have been reported. A study of the literature on these cases leads Crew to the conclusion that the recorded cases of abnormality of the reproductive system illustrate the process by which an individual, at one time possessing solely the complete sex equipment of the female, comes to exhibit the organization of the male. The sole female character which remains in what otherwise appears to be a typical male may be the full development of the Müllerian ducts, or the presence of ova amid the spermatic tissues. Such a transformed individual not only has the male organization but also behaves and functions as a male. It so happened that a transformed individual, functioning as a male, fertilized the eggs of a normal female. This male was one of an original population including 80% males. All (774) of his offspring which attained a sufficient development to permit identification of the sex were females. Including these 774 females, the tadpoles produced from the original population were 23% males and 77% females. This "swing-back" is taken as evidence which supports the conception that the frog has a chromosome constitution

of the XY, XX type, and that these cases of abnormality are females (XX), the chromosome constitution of which has become overridden by external factors, and which are "somatic" males or masculinized females. These, being XX in chromosome constitution, mating with normal females, also XX in constitution, will produce a generation consisting entirely of females. The presence of such "somatic" males in a population will thoroughly disturb the sex ratio of the succeeding generation, producing a "swing-back" which is a certain indication of their presence and reproductive activities. The mechanism by which the individual is thus transformed is one which acts through the internal secretions of the gonads. It is shown that in the frog the phenomenon of sex reversal is very similar to the same process in cattle, save that in the frog there is an antagonism of the sex hormones and that the ovarian is powerless in the presence of the spermatic. It is shown that there is a most intimate relation between the primary sex glands and the accessory sexual apparatus and the secondary sexual characters. Reasons are given for questioning the generally accepted opinion that Bidder's organ is a rudimentary ovary. References to 38 articles are given.

—R. G. H.

Rejuvenation and comparative researches on the incretory activity of the sex glands (Ringiovanimento e ricerche comparative sull' attività incretoria delle ghiandole sessuali). Declich (M.), Med. ital. (Milano), 1923, **4**, 674-687.

A general discussion.—P. M. N.

Tuberculosis and the endocrine glands. II. The ovary (Tubercolosi e ghiandole endocrine—Nota 2a: Ovaia). Gelmi (E.), Gior. di clin. med. (Parma), 1924, **5**, 251-262.

Castrated guinea pigs are more resistant to human tuberculosis, while those treated with ovary extracts are more receptive. On the contrary, animals castrated and treated with **thyroid** have as much resistance as those only castrated. In woman also some results have been obtained (as yet unconfirmed) indicating ovariotomy or sterilizing radiation of the ovary in tuberculosis.

—P. M. N.

Hormone sterilization of female animals. II. Injection experiments with corpeus luteum, ovary and placenta optones (Ueber hormonale Sterilisierung weiblicher Tiere. II. Injektionsversuche mit Corpus luteum, Ovarial und Placenta Opton). Haberlandt (L.), Arch. f. d. ges. Physiol. (Berl.), 1924, **202**, 1-13.

Injections of strong doses of corpus luteum optone into rabbits were without effect. Ovarian optones from pregnant animals produced a markedly positive result, and similar effects were produced by optones of the placenta obtained during the second half of pregnancy.—A. T. C.

The effect of the placenta on menstruation. Jacoby (A.), N. York M. J. & Med. Rec. (N. Y.), 1923, **115**, 619.

In order to test the theory that the internal secretory action of the placenta depresses the ovary and its allies, the authors administered placental extract in 5 gr. doses regularly three times a day for at least three months in a series of 25 cases in which menorrhagia was a prominent symptom. Four showed no change in menstrual function; the other 21 all showed a noticeable diminution of the amount of blood lost and the duration of the flow was usually reduced. The discomfort and pain during menstruation was considerably lessened in many instances. The blood pressure during the taking of the placental extract usually fell about 10 mm. No ill effects were reported from prolonged taking of this extract except in a few instances in which nausea and vomiting occurred. In spite of the small series, the large preponderance of successful cases lends encouragement to the view that the secretion of the placenta is effective in controlling the hyperactivity of the ovary and the glands aiding it in its function.—Am. J. Obst. & Gynec., **7**, 754.

Hormone sterilization of female animals (Ueber hormonale Sterilisierung weiblicher Tiere). Knaus (H.), Arch. f. d. ges. Physiol. (Berl.), 1924, **203**, 394-396.

Positive results were obtained in rats by repeated injections of corpus luteum extracts. The after litters were larger than usual (in three cases 19, 15 and 9), attributed to the delayed ripening of the follicles affected by the treatment.—A. T. C.

Experimental testicle transplants (Hodenverpflanzung in Tierexperimenten). Kurtzahn (H.), Arch. f. klin. Chir. (Berl.), 1923, **126**, 536.

These experiments, carried out on dogs, were partly transplants of portions of testicle into muscle, peritoneum, and so on, and partly injections of testicular substance by a paraffin syringe into similar tissues and into spleen and liver. These latter seem to succeed even better than direct implantations, but the final result in all alike is disappointing. The author concludes that both auto- and homotransplants in the dog always necrose; the peripheral parts of a mass last longer than the central, but the spermatogenous elements quickly disappear. When implanted by injection, the tissue has relatively a longer life but terminates in absorption. As there is no reason to think that grafts succeed better in man than in the dog, it appears that the good results claimed clinically for such grafts, if they have any organic basis at all, owe it to absorption of the tissue. If employed at all, transplantation by means of injection presents these advantages: substitution of a simple injection for a definite "operation"; elimination of infection; notably diminished damage to the host-tissue; good apposition and well-nourished sur-

face contacts; more rapid absorption of the necrosed portions; elimination of suggestion. Intramuscular injection is the best.
—Med. Sc., **10**, 317.

Can Steinach's doctrine concerning the function of the Leydig cells be considered as proof? (Ist Steinach's Lehre von der Funktion der Leydig'schen Zellen zwingend?). Kyrle (J.), Med. Klin. (Berl.), 1921, **17**, 1018, 1050-1052.

The author believes, in opposition to Steinach, that the interstitial cells of the testes are a "trophic auxiliary organ" for the incretory canalicular epithelium. The **interstitial cells** grow exuberantly and tend to regenerate after injury of the canalicular epithelium if a certain quantity of canalicular epithelium cells remain. There are remains of canaliculi even in cryptorchid testicles. When the epithelium of the canaliculi regenerates the interstitial cells degenerate again. The interstitial cells also make use of the superfluous nutritive material which was originally destined for the canaliculi, and deliver it again into the blood as a kind of incretion. After hematotoxic injury of the testicle (alcoholism, etc.) the interstitial cells do not grow because they are injured also. The interstitial cells are scanty before puberty and increase only with the beginning of spermatogenesis. During active spermatogenesis the Leydig cells decrease. The author has observed in the atrophic testicle of a four-year-old boy a group of perfectly developed canaliculi surrounded by Leydig cells and he believes that the canaliculi developed under the protective influence of accumulated interstitial cells. Ligation of the vas deferens causes augmentation of the interstitial cells only if the vessels are also injured. If the whole testicle is in a state of inferiority and reduced vitality vasoligation sometimes causes temporary rejuvenation.—A. B.

Interstitial cells in the testis of the rabbit after unilateral castration (Uber die Menge des Zwischengewebes im Hoden des Kaninchens nach einseitiger Kastration). Lipschütz (A.) & Ibrus (A.), Skandin. Arch. f. Physiol. (Leipz.), 1923, **44**, 237-247.

Unilateral castration in the young rabbit did not bring about any change in the relative mass of Leydig cells or their proportion to the total weight of the testicle 2½ to 14 months after operation.
—G. E. B.

Effect of ovariectomy and lutein injections on behavior of rats. Macht (D. I.) & Seago (D. W.), J. Comp. Psychol. (Balt.), 1924, **4**, 151-163.

The effect of ovariectomy and of injections of **corpus luteum** extracts was studied by Macht and Seago on the behavior of albino rats in the circular maze. Extirpation of both ovaries produced a distinct impairment in the muscular activity and general behavior

of the rats. Injections of small doses of ovarian extract, and more particularly of corpus luteum extracts, produced a distinct improvement in the running time and the cerebrospinal efficiency of both normal and ovariectomized rats, which improvement was noticeable soon after injection and was still present on the following day.
—J. Am. M. Ass., **83**, 66.

An ovarian graft; a case report. Miller (C. J.), N. Orl. M. & S. J., 1924, **76**, 547-548.

An ovarian isotransplant became swollen and painful and the patient developed metrorrhagia. The graft was removed. One end was cystic, the cyst containing about 100 cc. of clear fluid. An "active" **corpus luteum** was also found. Within a few days after removal of the graft the metrorrhagia ceased.—R. G. H.

Hermaphroditism in a 10-year-old subject [Hermaphroditismus (verus) glandularis alterans bei einem 10 jährigen Individuum]. Sand (K.), Skandin. Arch. f. Physiol. (Berl. u. Leipz.), 1923, **44**, 59-75.

Report of a subject 10 years old, brought up as a boy but showing at different times characteristics of male and female. Surgical exploration with histological examination of fragments taken from the gonads showed an **ovary** on one side and **testis** on the other.
—G. E. B.

Influence of the adrenals and ovaries upon precocious secondary sexual development. Siegel (A. E.), Arch. Pediat. (N. Y.), 1924, **41**, 265-272.

Two cases in girls are described to show that different glandular pathology may bring about a different yet somewhat related picture. One case is of a girl, 8 years of age, who died of general sarcomatosis after the removal of a sarcoma of the right ovary. She showed premature development of the secondary sexual characteristics, such as marked development of the mammae and the presence of labial genital hair. She was not massive or tall for her age. The other girl, 3 years of age, died of encephalitis and infective nephritis. She was large for her age, massive in her bony structure and in muscular development, her head was large and striking, leonine; the hair on the head was abundant. The genitalia were large and the pubic hair unusually developed. Autopsy showed a small suprarenal tumor of the right side which presumably was responsible for the precocious sexual development but which was not a factor in the production of death.—M. B. G.

The action of mammary gland extracts on the circulatory system and a study of their activity in animals (Azione degli estratti mammarî sul sistema circolatorio, e contributo alla conoscenza

del loro meccanismo d' azione nell' organismo animale). Spirito (F.), Rassegna di clin., terap. [etc.] (Roma), 1924, **23**, 31-41.

From physiological and clinical experimentation the author concludes that the activity of the mammary glands is due only to their endocrine relations with the **adrenals** and the **gonads.** The direct action on muscle and uterine vessels and on the circulatory system in general he believes to be insufficient in intensity and duration to produce any great effect.—P. M. N.

A case of massive hypertrophy of the breasts in a young girl. Wright (T.), Bull. Buffalo Gen. Hosp., 1924, **2**, 31.

Wright reports a typical case of puberty hypertrophy of the breasts, and calls attention to the fact that it may be due to an endocrine imbalance, whereby the normal inhibitory influence to mammary hypertrophy fails to act at the proper time.

—Am. J. Dis. Child., **27**, 652.

Preliminary report of a case of mixed sex. An apparent male, with a testis in scrotum on right side; ovary, tube and uterus in inguinal canal on left side. Young (H. H.), Johns Hopkins Hosp. Bull. (Balt.), 1924, **35**, 165-168.

The case is reported of an individual operated upon for removal of a mass, supposedly an undescended testicle, in the inguinal canal. The mass proved to consist of an ovary, uterus and Fallopian tube. On the opposite side was found in the scrotum a testicle, somewhat undeveloped (as shown by microscopic examination). Psychologically, the subject was normally masculine. The penis was normal in size, but with congenital chordee. The urinary meatus was a cleft in the scrotum. Hair growth and distribution were normally masculine. It is stated that this is the first human case of true lateral glandular hermaphroditism recorded. Unlike all the lateral hermaphrodites found in animals, this patient was masculine externally, though he had inactive tubules and a functioning ovary. The interstitial cells were, however, apparently hyperplastic and no well developed lutein cells were seen.—R. G. H.

Case of dystrophia adiposogenitalis in a child two years of age, with results of seven months' treatment. Boyd (C. S.), Arch. Pediat. (N. Y.), 1923, **40**, 736-746.

This boy was marasmic until 18 months of age. When first seen by the author at the age of 2 years he presented a typical picture of Froelich syndrome with some signs of **hypothyroidism.** Under intensive treatment, consisting of whole pituitary substances and thyroid, he improved to a great extent, the improvement being more pronounced in those symptoms which were due to hypothyroidism and to a lesser extent in those due to dyspituitarism.

—M. B. G.

Two cases of diabetes insipidus cured by injections of extract of the posterior lobe of the hypophysis (Deux cas de diabète insipide gueri par les injections d' extrait de lobe postérieur d'hypophyse). Denechau (D.) & Mandroux (J.), Bull. et mém. Soc. méd. hôp. de Par., 1924, **48**, 561-566.—F. S. H.

A "forme fruste" of dystrophia adiposogenitalis and its experimental allocation (Ueber eine Forme fruste der Dystrophia adiposogenitalis und ihre experimentelle Begründung). Dietrich (H. A.), Ztschr. f. Geburtsh. u. Gynäk. (Stuttg.), 1924, **87**, 146-156.

In cases of "forme fruste" dystrophia adiposogenitalis 1 cc. of adrenalin produces an abnormal type of blood sugar curve during the first hour after administration. The first reaction is a fall. This is followed by a rise.—F. S. H.

Biological tests of hypophysis extracts: action on the crest of the cock (I saggi biologici degli estratti di ipofisi: azione sulla cresta del gallo). Di Mattei (P.), Riv. osp. (Roma), 1924, **14**, 105-118.

A criticism of the methods of standardization of hypophysis extract. The author proposes as a practical, constant and sufficiently exact test cyanosis of the crest and wing of the cock. He advises endovenous application of 0.0025 gm. fresh posterior lobe in the wing. The reaction is completed in about an hour, and in 3 hours the same animal can be experimented on again. The cock is very resistant to large doses.—P. M. N.

Tumor of the hypophyseal stalk. Fraser (J.), Edinb. M. J., 1924, **31**.

Fraser showed a case of developmental tumor of the hypophyseal stalk in a girl, aged 9 years. The symptoms were adiposity, squint, headache, and deterioration of vision. The roentgenogram revealed a calcified, partly cystic epithelial tumor of the stalk, producing a deficiency of the anterior lobe, with Frölich's syndrome, also interruption of the right optic tract with irritation of the third cranial nerve and an increase in intracranial tension. The only suitable treatment in this case seemed to be decompression, which was done, with considerable improvement resulting.

—Am. J. Dis. Child., 28, 112.

The influence of pituitrin on diuresis (Zur Kenntnis der Pituitrinwirkung auf die Diurese). Molitor (H.) & Pick (E. P.), Arch f. exper. Path. u. Pharmakol. (Leipz.), 1924, **101**, 169-197.

Experiments were made on dogs with a bladder fistula, and the excretion of urine was studied after administration of 250 cc. of water by mouth. Subcutaneous injections of small doses of pituitary extract suppressed diuresis, whether given before or after

the excretion of this water began. In no case was increased diuresis observed. The anti-diuretic action was observed in dogs with Eck-fistula, and was not affected by inhalation of amyl nitrite, injection of ergotamine, sodium nitrite, papaverine, phlorhizin, nitroglycerin, caffeine, or thyroid extract. The effect does not appear to be produced, therefore, by vascular changes, especially as it lasts for many hours, whereas the vascular effects of pituitary are fleeting. The failure of thyroid extract to restart a diuresis stopped by pituitary is interesting in view of Eppinger's demonstration of the value of thyroid administration in edema. Injection or oral administration of urea and hypertonic salts will, however, restart a diuresis.—Physiol. Abst., **9**, 134.

Hypophyseal extract and diuresis (Azione dell'estratto ipofisario sulla diuresi nella pratica infantile). Misasi (M.), Pediatria (Napoli), 1922, **30**, 819-822.

Pituitrin in normal children causes concentration of the urine sooner than in adults. The chlorides increase in direct ratio with the specific gravity. In kidney diseases concentration is not obtained so soon; the urine remains concentrated longer and the chlorides diminish. In atrophy no variation in the specific gravity is obtained.—G. V.

Influence of diet on insulin action (Ueber den Einfluss der Ernährung auf die Wirkung des Insulins). Abderhalden (E.) & Wertheimer (E.), Arch f. d. ges. Physiol. (Berl.), 1924, **203**, 438-342.

Rats fed chiefly on a fat diet do not show the typical hypoglycemic convulsions following injection of insulin. Rats fed chiefly on protein also are unaffected, though animals on mixed fat-protein-carbohydrate diet are affected as usual. Rats in the convulsion stage show a rectal temperature of 23° or less. Animals fed fat or protein do not show such low temperatures. In these animals three times the lethal dose of insulin scarcely produces any symptoms. Frogs are very resistant. Twenty units injected into the dorsal lymph sac of a 53 gram frog produced no marked symptoms. Pigeons and guinea-pigs show a similarly great resistance.

—A. T. C.

Functioning of the fetal pancreas after ablation of the maternal pancreas (Functionnement du pancréas foetal apres ablation du pancréas maternel). Aron (M.), Stulz (E.) & Simon (R.), Compt. rend. Soc. de biol. (Par.), 1923, **89**, 571-573.

In the absence of the maternal pancreas, before the islands of Langerhans begin to function in the fetus, mother and fetus present hyperglycemia. After development of the islands the mother presents hyperglycemia, while the fetus is protected.

—T. C. B.

An insulin-like material in various tissues of the normal and diabetic animal. Best (C. H.), Smith (R. G.) & Scott (D. A.), Am. J. Physiol. (Balt.), 1924, **68**, 161-182.

Insulin is present in various tissues other than the pancreas. It is present in reduced amounts in completely depancreatized dogs.
—T. C. B.

Preliminary report on the effect of insulin on the rate of heat production and its significance in regard to the calorigenic action of adrenalin. Boothby (W. M.) & Wilder (R. M.), Med. Clin. N. Am. (Phila.), 1923, **7**, 53-56.

This is a report on the results of 4 experiments on the effect of insulin on the rate of heat production of one normal person and three diabetic patients under standard postabsorbitive basal conditions. It is determined by these observations that insulin is not a calorigenic agent like thyroxin with a delayed reaction, nor, probably, does it in itself possess an immediate calorigenic action like adrenalin.—I. B.

Studies of intermediary carbohydrate metabolism and insulin. I. Studies on normal animals (Studien über intermediären Kohlenhydratumsatz und Insulin. I. Versuche an Normaltieren). Brugsch (T.), Benatt (A.), Horsters (H.) & Katz (R.), Biochem. Ztschr. (Berl.), 1924, **147**, 117-149.

Studies of the respiratory exchange are insufficient to determine the mechanism of the action of insulin; studies of the intermediary metabolism of the carbohydrates are necessary. To this end a method was devised by which the intermediary processes in the liver, muscles and other organs could be studied immediately after death. The method consists in suspending the finely divided tissues in aerated, sugar-containing Ringer's solution. Observations were made on normal animals, animals which had been fasted for 24 hours and animals in which hypoglycemia had been produced by insulin. The course of the intermediary changes was followed by determinations of the glycogen content of the organs, the formation and disappearance of glucose with or without the formation of lactic acid, the formation of hexose phosphoric acid and intermediate products. It was found that the normal liver forms only glucose and a bit of lactic acid; that the liver from fasted animals changes glucose to lactic acid, and that after insulin poisoning there occurs a marked glucose deficit along with the formation of hexose phosphoric acid and intermediary sugars. From this it is apparent that insulin effect is in the nature of an activation of an oxidizing-synthesizing process in liver and muscle. Insulin is not simply a neutralizing antagonist of the liver diastase, but is an antagonizing synergist.—F. S. H.

A method of titration of insulin (Sur un mode de titration de l'insuline). Desgrez (A.), Bierry (H.) & Rathery (F.), Bull. gén. de thérap. (etc.) (Par.), 1924, **175**, 97-102.

Dissatisfied with the physiological assay of insulin as an index of its efficacy in diabetes, as based on the "rabbit-unit," the authors proposed that the substance be evaluated on the basis of dry weight of preparation as a purified and sterile powder. The standard of such preparation should be that the injection of 5 mg. per kilo body weight into a dog fasted for 24 hours produces during the ensuing 2 hours a 40 to 50% lowering of the arterial blood-sugar. —F. S. H.

The effect of insulin on the oxygen and carbon dioxide tensions in air between the skin and the muscles. Campbell (J. A.) & Dudley (H. W.), J. Physiol. (Lond.), 1924, **58**, 348-354.

The curve for oxygen tension in air injected under the skin follows the blood sugar after insulin. There is an increase of carbon dioxide tension also, lasting an hour or two.—T. C. B.

Action of insulin (Sur quelques modalités d'action de l'insuline). Desgrez (A.), Bierry (H.) & Rathery (F.), Compt. rend. Soc. de biol. (Par.), 1923, **80**, 473-475.

Animals react differently to the same dose of insulin. Variations of hypoglycemia in the same animal are not proportional to the dose of insulin. Liquid extracts cause a toxicity which is independent of the hypoglycemic effect. There is an individual optimal dose, beyond which no advantage is gained.—T. C. B.

Influence of insulin on the vasoconstriction of the liver (Zur Wirkungsweise des Insulin als Vasokonstriktion der Lebergefäsze). Freund (E.), Wien. klin. Wchnschr., 1923, **36**, 528-529.

More than 10 years ago the author demonstrated that ether and alcoholic substances could be isolated from the pancreas which caused marked vasoconstriction in the surviving liver of the dog. Extracts of muscle and testicle did not produce this constriction. When the liver was perfused with Ringer's solution and insulin was added the rapidity of perfusion sank markedly. Insulin, therefore, produces vasoconstriction of the liver and increases the resorptive power of the liver cell. This does not prevent insulin from having other properties also.—J. K.

The behavior of the blood lipoids after fat feeding in normal and diabetic subjects with and without the administration of insulin (Ueber das Verhalten der Blutlipoide unmittelbar nach Fettzufuhr bei normalen und zuckerkranken Menschen, mit und ohne Anwendung von Insulin). Hartmann (H. U.), Biochem. Ztschr. (Berl.), 1924, **146**, 307-317.

The administration of glucose causes no change in the total lipoid content of the blood. When 50 grams of butter and 20 grams of cereal are fed to normal and diabetic subjects the lipoids of the blood increase during the first hour and then gradually fall back to the fasting level within the succeeding 4 hours. When insulin (50 units) is given one hour before the fat feeding it may be followed by a tendency to a decline in the total lipoid content of the blood; when the test meal is then given one hour after the insulin the total lipoid content of the blood usually increases as after the test meal not preceded by insulin.—F. S. H.

Action of insulin. I. Sugar formation in the surviving frog liver (Beiträge zur Wirkung des Insulins. I. Zuckerbildung der überlebenden Froschleber), v. Issekutz (B.), Biochem. Ztschr. (Berl.), 1924, **147,** 264-274.

When insulin is added to the perfusion fluid it fails to influence sugar formation by the surviving liver of the frog. If, on the other hand, the frog has been treated the day before with insulin its liver shows a decrease in sugar-forming ability of from 20 to 25 per cent, and reacts less to **adrenalin.**—F. S. H.

The effect of insulin on the phosphoric esters in blood and muscle. Kay (H. D.) & Robinson (R.), Chem. & Industry Rev., 1924, **43,** 313.

During an investigation of the action of the phosphoric esterase shown to be present in bone on the acid-soluble phosphorus compounds in blood, muscles, and other tissues, it was found that the amount of organically bound phosphate contained in rabbit muscle, which is readily hydrolysed by this enzyme, was increased by 15-25% above the normal when insulin had been previously injected and the animal was killed at or just before the onset of convulsions. Similar results were obtained by estimating the increase of inorganic phosphate in the muscle extracts after autolysis, as in Embden's "lactacidogen" determination. Assuming that the conclusion arrived at by Embden and his collaborators, that the lactacidogen of muscle is a hexose phosphoric ester is correct, the discovery of a definite increase in this substance after insulin affords a probable explanation of the fate of the sugar which disappears from the blood and which, it is known, is neither transformed into glycogen nor fat. The increase actually found would account for about three times the amount of sugar which disappears from the blood, but in this calculation no allowance is made for any mobilization of sugar from glycogen or other reserves. These results agree with those just published in abstract by Wagner and Andova, who, using a slightly different method, find about the same increase in "lactacidogen" after insulin.

—Chem. Abst., **18,** 218.

Radiographic study of arterial lesions in diabetics (Les lésions artérielles des diabétiques décelées par la radiographie). Labbé (M.) & Lenfantin (H.), Bull. et mém. Soc. méd. d. hôp. de Par., 1924, **48**, 522, 524.

Radiography is found to be of help in determining the extent of arterial lesions in diabetics. The opacity is assumed to be due to deposition of calcium salts.—F. S. H.

The skin reaction to tuberculin in diabetes (La cuti-réaction à la tuberculine chez les diabétiques). Labbé (M.) & Boulin (R.), Bull. et mém. Soc. méd. d. hôp. de Par., 1924, **48**, 701-702.

From tests on 12 diabetics and 12 controls it is concluded that diabetes leads to an attenuation of the usual reaction to tuberculin. — F. S. H.

Some variations in the acid-base balance of the blood in disease. Myers (V. C.) & Booher (L. E.), J. Biol. Chem. (Balt.), 1924, **59**, 699-712.

The uncompensated acidosis of severe **diabetes** promptly responds to the administration of **insulin** as indicated by the rise in plasma pH and bicarbonate.—F. S. H.

Insulin and phlorhizin diabetes. Nash (T. P.), J. Biol. Chem. (Balt.), 1923, **58**, 453-462.

Fasting female dogs were used. They were phlorhizinized and then treated with insulin. There was a marked diminution in nitrogen excretion following the administration of insulin. Either a specific retention of nitrogen or a protein sparing action has been produced. The latter interpretation is favored. Sugar was withdrawn from the blood under the influence of insulin and consequently the sugar excretion in the urine was lowered. On the other hand, this lowered excretion was followed by an increase which indicates to Nash that the sugar so withdrawn was surrendered to the blood again. These findings are taken as corroboration of the view of Benedict and Nash that phlorhizin effects an intrinsic impairment of utilization of sugar by the tissues.—F. S. H.

The value of insulin in the utilization of carbohydrates. Olmsted (W. H.) & Kahn (S. H.) with the assistance of Case (Eleanor) & Taussig (Nan), Boston M. & S. J., 1924, **190**, 1018-1028.

Thirteen cases of **diabetes** were studied to determine whether there is any relation between the amount of insulin given and the amount of carbohydrate utilized. The authors concluded from their results, which are given very fully in a series of tables, that (1) "It is possible to demonstrate under the conditions outlined a quantitative relationship between insulin administered and carbohydrate

tolerated, one unit of 'H' insulin being equivalent to 1.4 grams of carbohydrate; (2) in the majority of diabetics, sugar derived from protein shows the same quantitative relationship to insulin as that derived from starch. Of the 9 diabetics on whom feeding excess of protein was studied, 3 showed very disastrous effects."—J. C. D.

The technic of blood-sugar estimation as done at the Memorial Hospital of Philadelphia. Petty (O. H.) & Sherrill (W. P.), Internat. Clin. (Phila.), 1923, **3** (series 33), 22-28.

After returning to their homes following **insulin** treatment, most patients require periodical blood-sugar examinations. As many patients live at a considerable distance from a well-equipped laboratory, Petty and Sherrill chose the Benedict modification of the Lewis-Benedict method of blood-sugar estimation because the picrate solution employed acts as a preservative preventing glycolysis during transportation of the specimen. A description of the taking of the blood from the patient at a distance from the hospital, as well as the technic of the blood-sugar determination, constitutes the major portion of this article.—I. B.

Blood sugar regulation and its importance in the pathogenesis of diabetes mellitus (Ueber Blutzuckerregulation und ihre Bedeutung für die Pathogenese des Diabetes mellitus). Pollak (L.), Med. Klin. (Berl.), 1921, **17**, 925-930.

The blood-sugar level is kept constant by a nervous hormone regulation mechanism. A hormone irritation of the blood can cause sugar excretion from the liver. **Adrenalin** does not seem, therefore, to be a physiological factor in blood-sugar regulation. The blood acidity caused by lactic acid which is produced in the muscles is said to excite the liver to mobilize sugar, but the liver mobilizes sugar even if no acidification takes place and if the sugar is utilized only for building up tissues. The author supposes that every digression of the blood-sugar level over or under the normal causes activity of the regulation mechanism. This level remains almost normal in phlorizin diabetes even after paralyzing the sympathetic ends by ergotoxin. Temporary sinking of the sugar level excites the liver to mobilize more sugar; temporary rising tends to cause sugar consumption. Hyperglycemia also checks sugar production in the tissues. Intravenously administered glucose (35 gr.) disappears from the blood in 15 minutes. Cardial and nephritic transudations have the same sugar level as the blood. Nearly all kinds of hyperglycemia, with the exception of diabetes mellitus, depend on nervous central or peripheral irritations. The parasympathetic system has almost no influence. The nervous system is not a necessary factor in blood-sugar regulation, but the liver and the entire endocrine apparatus are. After extirpation of the adrenals the blood sugar sinks and disappears completely, but it may be in-

creased again by piqûre, and the capability to mobilize sugar is not lost. The blood-sugar level in diabetes mellitus is high and of pathological lability, depending on diet, muscle activity, etc. In diabetes mellitus there is probably no decreased capability to consume sugar within the tissues (isolated organs of depancreatized animals consume sugar normally) but there is no irritation by the pancreas hormone causing sugar consumption. Even the capability of the liver to produce glycogen is not altered. The transformation of glycogen into sugar within the liver is increased in diabetes mellitus and is the most essential factor of it. The liver of depancreatized animals delivers abnormally much sugar into a perfusing liquid, not in consequence of nervous irritation, but of an alteration of the blood sugar regulation. There is decreased reaction of the liver upon variation of the blood-sugar level. Nephrectomy in a depancreatized dog causes the blood sugar to rise; phlorizin has the opposite effect, while in the normal animal a constant level is conserved. The sugar production in the liver of depancreatized animals may be increased by piqûre and adrenalin or decreased by opium, etc. The production of amino, keto and fat acids, which act similarly to adrenalin, incites the hypersensitive diabetic liver to mobilize glycogen. Albumin has a similar effect. Sugar oxidation and glycogen production are thus not primarily altered in diabetes mellitus, but there is an alteration of their regulation. In diabetes mellitus there is not properly, therefore, an alteration of carbohydrate metabolism.—A. B.

The influence of lack of sleep on assimilation of sugar (Beiträge zur Diabetesforschung. VI. Mitt. Uber den Einflusz des Schlafmangels auf die Zuckerassimilation). Sakaguchi (K.) & Asakawa (O.), Mitt. a. d. med. Fakult. d. k. Univ. zu Tokyo, 1922, **28**, 515-526; abst., Ber. ü. d. ges. Physiol. (Berl.), 1923, **18**, 82.

The blood-sugar curve was established in healthy and in diabetic subjects after administration of equal amounts of carbohydrates and other foodstuffs, both after a good normal sleep and after a sleepless night. It was shown that neither sleeplessness nor mental strain reduced the tolerance for carbohydrates of healthy or of diabetic subjects.—R. G. H.

Treatment of diabetics with low threshold of sugar elimination (Beiträge zur Diabetesforschung. VII. Mitt. Uber die Behandlung von Zuckerkranken mit niedriger Zuckerausscheidungsschwelle). Sakaguchi (K.), Asakawa (O.) & Ueda (H.), Mitt. a. d. med. Fakult. d. k. Univ. zu Tokyo, 1922, **29**, 179-203; abst., Ber. ü. d. ges. Physiol. (Berl.), 1923, **18**, 82.

Diabetic subjects have been described in whom the urine was sugar-free, but in whom small amounts of sugar (under 1%) would appear in the urine on administration of 50 to 100 gm. of rice.

According to Bang, the excretion of sugar takes place only if the blood sugar reaches a height of 0.12 to 0.14%. It is therefore treated as a very low threshold of sugar elimination, yet the author assumes that it is not a question of renal diabetes since in a fasting condition the urine is sugar-free. In such cases, glycosuria has no harmful influence on carbohydrate tolerance. Strict dietary limitation is therefore unnecessary and may even become harmful. The author believes that in such cases not only should the sugar elimination be considered, but also the threshold of sugar elimination.—R. G. H.

Ketosis and carbohydrate metabolism. Shaffer (P. A.), Ann. Clin. Med. (Balt.), 1924, **3**, 93-95.

A brief summary of Shaffer's conception of ketogenic balance. Carbohydrate is used both for fuel and for supplying an intermediate product in the oxidation of fats. When the latter process fails ketone bodies appear in the urine. Fats are therefore "ketogenic." Carbohydrate, similarly, in that it aids in complete oxidation of fats, is "antiketogenic." Glycosuria without diacetic acid in the urine shows that the carbohydrate tolerance is lower than the carbohydrate ingested but is not so low as to provide a negative ketogenic balance. If there is both sugar and diacetic acid in the urine the carbohydrate tolerance is so low that, at the rate of that subject's total metabolism—the rate at which the subject is living—a ketogenic balance cannot be maintained, and anything that disturbs it further may produce a marked acidosis and coma. The danger line is crossed. The patient should be in bed and probably will need **insulin.** If, on the other hand, there is ketosis without glycosuria it probably means merely that the glucose or carbohydrate supply is insufficient to provide a ketogenic balance and that that is not due to a lowered carbohydrate tolerance.—R. G. H.

Glycolysis in bloods of normal subjects and of diabetic patients. Tolstoi (E.), J. Biol. Chem. (Balt.), 1924, **60**, 69-75.

The glycolytic power of 8 normal subjects and 11 diabetics was studied. Some of the bloods were studied both at room temperature and at 37° C. Aseptic precautions were used and the red and white cells counted. In the reported series of observations, no diminution in the glycolytic power of diabetic bloods was found when compared with that of normal subjects when the bloods were kept at 37°. It was also found that at room temperature the glycolytic rates were definitely diminished in both types of blood.—F. S. H.

The physiological action of insulin (Ricerche sul l'azione fisiologica dell' insulina—2a nota). Serono (G.), Torcello (E.) & Cruto (A.), Rassegna di clin., terap. [etc.] (Roma), 1924, **23**, 53-60.

This investigation brings to light new functions of insulin, rec-

ognizing in it a neutralizing action on excess digestive ferments. According to this theory the action of adrenalin is antagonistic to the external secretion of the pancreas and to the digestive ferments in general.—P. M. N.

Total inorganic calcium and phosphorus in the blood of diabetic patients showing a peculiar symptomcomplex. Smith (B.) & West (H. F.), Tr. Am. Soc. Clin. Investigation, 1924.

A considerable proportion of patients with diabetes develop a rather definite group of symptoms, which become manifest after they have reached a state of apparently adequate nutrition. These symptoms may reach a point of distressing severity. Prominent in this symptom complex are attacks of weakness (at times approaching collapse), sweating, coldness, nervousness, paresthesias and stiffness of muscles; with the finding of vascular hypotension, rapid pulse, pallor, cold moist skin and poor muscle tone. In occasional instances are seen attacks suggesting mild tetany. This complex occurs most frequently among patients who had become radically undernourished or who previously have had vigorous treatment for some acute diabetic emergency. It occurs among patients who have been treated without insulin, but has been encountered more frequently among those who have had this assistance. True hypoglycemic reactions have been excluded by blood and urine analyses. The finding of a low blood calcium in a few of the patients with more marked symptoms, with a certain amount of relief from calcium feeding, has led to a study of the total inorganic calcium and phosphorus of the blood. As a rule, blood was taken just before the noon meal, which was usually not at the time of acute symptoms. In 25 determinations on 20 patients in good physical condition and not showing these symptoms, total calcium of below 10 mg. per hundred cubic centimeters was found in but two, and these had previously experienced similar symptoms, but were vigorous and doing manual work at the time of examination. The average for the series was 11.45 mg. In 29 determinations on 23 patients showing symptoms similar to the foregoing, only 7 showed calcium of 10 mg. or above. The average calcium of this series was 9.01 mg., with 6.4 mg. as the extreme low finding. Total inorganic phosphorus showed practically the same distribution in the two series, averaging 3.54 mg. and 3.57 mg., respectively. While the evidence is not sufficient to warrant the assumption that calcium disturbance is the sole or primary factor in this symptom complex, the findings seem of definite significance and are offered as a partial study of the condition.—J. Am. M. Ass., **82**, 1990.

On the preparation of insulin. Somogyi (M.), Doisy (E. A.) & Shaffer (P. A.), J. Biol Chem. (Balt.), 1924, **60**, 31-57.

A simplified method is described for the preparation of insulin

from beef pancreas. The activity of insulin is probably a property of an individual protein "insulin-protein," the solubility of which is described. The method of extraction from the pancreas and its purification is considered from the point of view of the properties of the "insulin-protein." It has been separated from two other proteins which are also precipitated at their isoelectric points, and which are included in the preparations of insulin, purified by "isoelectric precipitation" as earlier described by the authors. Data are given to indicate the activity of the purified "insulin-protein."

—F. S. H.

The relation between the histological state of segments of transplanted pancreas and glycosuria (Sui rapporti che passano fra lo stato istologico dei segmenti di pancreas trapiantati e la glicosuria). Visco (S.), Arch. di Farmacol. sper. (Roma), 1923, **35**, 154-160; 167-183.

Histological report of 8 cases of pancreas transplantation, 4 subjects with and 4 without glycosuria. The author thinks that the incretory function of the pancreas should be attributed to the whole organ.—P. M. N.

Present status of diabetic patient as surgical risk. Wilder (R. M.) & Adams (S. F.), Wisconsin M. J. (Milwaukee), 1924, **22**, 557-561.

Wilder and Adams stress the fact that the formerly prohibitive mortality which accompanied attempts at surgery on diabetic patients has been materially reduced by skillful surgery, proper anesthesia and the judicious use of medical measures before and after operation. It is unjustifiable to subject a diabetic patient to surgery unless very good surgery and special medical supervision are available. **Insulin** is a valuable adjunct in the management, but is only one of several important medical measures and will not protect a patient unless it is skillfully administered. An operation may provoke severe acidosis in cases of very mild diabetes, and such cases deserve, therefore, the same scrupulous medical attention as do those of severe diabetes. Three hundred and twenty-seven operations are reported on 251 diabetic patients with four deaths. This gross mortality of 1.2% by operation compares favorably with that of the general surgical list. One hundred and forty-one of the operations were major surgical procedures.

—J. Am. M. Ass., **82**, 2084.

The biochemistry of experimental tetany. Creatin of urine and muscle in guanidin and parathyroid tetany with and without calcium treatment (Zur Frage der Biochemie der experimentelle Tetanie. Harn und Muskelkreatin bei der Guanidin und Parathyreopriven Tetanie ohne und nach Ca-Behandlung). Palladin (A.) & Griliches (L.), Biochem. Ztschr. (Berl.), **146**, 458-466.

It was found that the creatin content of muscle was increased in tetany due to guanidin and to parathyroid deficiency. This increase in muscle creatin gives rise to creatin in the urine, while the creatinine excretion either is increased only slightly or not at all. The experiments show a direct relation between creatin formation in muscle and the creatin and creatinine excretion in the urine. When calcium is given to the guanidine treated rabbits creatin excretion is within normal limits; and the creatin content of the muscles is normal if the symptoms of tetany are aborted. This leads to the conclusion that Paton's theory that the increase of creatin is due to formation in excess amounts from guanidine is wrong.—F. S. H.

Blood changes and clinical symptoms following oral administration of phosphates. Salvesen (H.), Hastings (A. B.) & McIntosh (J. F.), J. Biol. Chem. (Balt.), 1924, **60**, 311-326.

Experimental results are presented which lead the authors to the conclusion that the clinical symptoms of tetany produced by the oral administration of phosphates to dogs are due to a reduction of the blood calcium. From this it is stated that "the symptoms of parathyroid insufficiency are due to the low blood calcium."

—F. S. H.

Pineal gland tumor. Jess (J. H.), Tr. Chicago Pediat. Soc., 1924.

This boy, aged 21 months, was of normal birth, with spontaneous delivery. He was breast-fed for 13 months, and developed normally but learned to walk very slowly. He was first seen when 15 months old, when he was able to stand up and walk around a chair. He was beginning to talk. His mother first noticed that he had pubic hair at about this time, and that the genitalia were larger than normal. His voice has always been very coarse, and all measurements are in excess of the average for his age. His head is larger than normal and the features are those of a much older child. Pubic hair is present. The right testicle is about the size of a walnut, the left about two-thirds that size. There is no evidence of a tumor mass, although one is much firmer than the other. Roentgenologic examination of the head and sella turcica gave negative findings. There are no focal findings, such as might be due to intracranial pressure. There is no nystagmus, no paralysis of the eye muscles. The sight is good and the fundi are normal. There is no evidence of involvement of the suprarenals, and while the genitalis are much more advanced in their development than is normal for his age, the size and shape of the skull and retarded mental development have led the author to believe that there was some intracranial pathologic change. The Wassermann and tuberculin tests are negative. Clinical reports of similar cases show that in most instances homosexual changes in the male have followed tumors of the pineal gland, while heterosexual changes have

been secondary to involvement of the suprarenalis.—Am. J. Dis. Child, **28**, 123.

Status thymicolymphaticus. Delgado (H.), Rev. de psiquiat. y discip. conex., 1924, **5**, 40-55.

The author discusses the different factors in this condition, especially its etiology, pathology and diagnosis. The clinical symptoms are described, particularly those of pluriglandular origin and the vago-sympathetic disturbances. Among the syndromes due to status thymicolymphaticus Delgado points out its close relation to epilepsy and reports some protocols to this effect. He reports, too, a case of mors thymica and discusses some of the theories attempting to explain it.—A. M. Q.

Physiological and therapeutic importance of the thymus (L'importanza fisiologica e terapeutica della ghiandola timo). Gagliardi (A.), Terapia (Milano), 1924, **14**, 47-53.

A report of observations on the physiological action of the thymus, with particular consideration of its relation to tuberculosis. —P. M. N.

The diagnosis and treatment of enlarged thymus. Grier (G. W.), Am. J. Roentgenol. (N. Y.), 1924, **11**, 141-144.

One should be on the alert for enlarged thymus in young infants, especially in those of premature birth. Heavy breathing, a crowing inspiration and later on a failure to thrive should direct suspicion to this condition. It should be remembered that the thymus enlarges greatly when the baby cries. Radium treatment is practically a specific. The dosage required to produce a favorable result is not large and the author says that the thymus can be sufficiently reduced without producing an erythema of the skin. There are many minor differences in technique which do not materially alter the final result, but if one follows a prescribed technique he should adhere to it strictly. The main factors governing dosage are the quantity of radium used, its distribution, whether in one or several capsules, the distance from the skin and the number of areas treated. "One hundred milligrams of radium in one capsule and moved about over different areas has a different effect from the same quantity divided into four capsules of 25 mg. each and scattered about over one area, even if the same distance from the skin and the same number of milligram hours are used. It should be remembered that where adjoining areas are exposed, such area receives a part of the dose when the adjacent area is exposed. In ordinary sized area of about one by two inches this extra dosage amounts to about one-quarter of the dose applied to each area, so that if other adjoining areas are treated, each area receives exactly twice the dose directly applied to it. The technique which I have

used satisfactorily for some time is to place four tubes of radium, each containing 25 mg., in a wooden block with holes bored in it one inch apart to contain the capsules. The filter used is one millimeter of brass. The block is left in position for ten hours with the radium at a distance of three-fourths of an inch from the skin. This dose does not produce any erythema, and usually one treatment is all that is necessary, although occasionally it has to be repeated. It is an entirely safe dose and can be increased to twelve or fourteen hours if desired, although I have not considered it necessary."—J. Radiol., **4**, 181.

Relation between the thymus and the genital organs (Beitrag zur Physiologie der Thymus. Uber die Beziehungen zwischen Thymus und Generationsorganen). Knipping (H. W.) & Rieder (W.), Ztschr. f. d. ges. exper. Med. (Berl.), 1924, **39**, 378-384.

Should guinea pigs after coming to puberty be divided, some being cut off from sexual intercourse and others induced to vigorous sexual activity, the average weight of the thymus of the animals kept separate is about 27% higher than that of the animals to which sexual activity has been allowed. Histologically the point at issue is that the abstaining animals show a simple persistence without sign of general or specific hyperplasia, while the glands of the other animals show physiological involution.—Physiol. Abst., **9**, 183.

The diagnosis of enlarged thymus by the x-ray and treatment by x-ray or radium. Pfahler (G. E.), Arch. Pediat. (N. Y.), 1924, **41**, 39-46.

The thymus can be enlarged without producing symptoms and, on the other hand, thymic symptoms may develop even when no enlargement of the thymus is shown by the x-ray. For by the x-ray we can show only lateral enlargement and yet it is the anterior-posterior pressure which causes the symptoms. The therapeutic test is more reliable than the x-ray diagnosis, as in nearly all cases the symptoms are relieved by radiation. Lymphadenitis of the upper mediastinum in some instances resembles very closely enlarged thymus of slight degree. The shadow in these mild cases is not characteristic and therefore it is difficult to make a positive diagnosis. Both thymic enlargement and lymphadenitis yield to radiation. Heavy breathing, wheezing or crowing respiration, cyanosis or an abnormal cry should direct attention to the thymus. The thymus enlarges when the baby cries. X-ray or radium treatment is a specific, but must be applied with caution, accuracy and skill. Radium is probably preferable and safer and when one considers that only one application is necessary it is probably as cheap.

—M. B. G.

The influence of thymus extracts on capacity for work and fatigability of mammalian muscle (Ueber den Einfluss von Thymusextrak-

ten auf die Leistungsfähigkeit und Ermüdbarkeit des Säugetiermuskels). Thurner (K.), Arch. f. d. ges. Physiol. (Berl.), 1924, **202**, 444-467.

Intravenous injection of thymus extracts produces a distinct increase in the work capacity of fatigued striped mammalian muscle. The alcohol extract is especially active; its active principle is thermostable. Alcohol extracts of other organs do not produce the effect. Choline is not the active principle. The action on unfatigued muscle is uncertain, and in any case slight.—A. T. C.

Substances with specific action prepared from single organs IX. (Studien über die von einzelnen Organen hervorgebrachten Substanzen mit spezifischer Wirkung IX.). Abderhalden (E.) & Schiffmann (Olga), Arch. f. d. ges. Physiol. (Berl.), 1923, **198**, 128-144.

It is not possible to influence the metamorphosis of tadpoles either by feeding frogs with thyroid before spawning, by treatment of unfertilized eggs and sperm with active substances, or similar treatment of fertilized eggs. Tadpoles show typical thyroid action after feeding any of 3, 5-l-diiodotyrosine, 3, 5-d-l-diiodotyrosine, iodized silk peptone, thyroglobulin, or iodoalbumen D, iodoserumalbumen A and D (Blum and Strauss' preparations). Tyosine plus potassium iodide, dibromtyrosine, phenylalanine, p-iodophenylalanine, and silk peptone are all without action. Tadpoles which show the typical action of thyroid have a lessened liver glycogen content. —A. T. C.

Gas metabolism and metamorphosis of amphibian larvae after feeding thyroid or iodine containing substances (Gaswechsel und Metamorphose von Amphibienlarven nach Verfütterung von Schilddrüse oder von jodhaltigen Substanzen). Abelin (I.) & Scheinfinkel (N.), Arch. f. d. ges. Physiol. (Berl.), 1923, **198**, 151-163.

Thyroid feeding to larvae of Rana esculenta and of Axolotl, leads to accelerated metamorphosis, with decreased carbon dioxid production (50 to 70% of normal) during the metamorphosis period. Di-iodotyrosine and di-iodotyramine produce similar results. Initially, in all cases, there is a slight rise in carbon dioxid output, and it is suggested that this increased gas metabolism may be the actual stimulus leading to the metamorphosis. Iodine does not accelerate metamorphosis in axolotls.—A. T. C.

Thyroid treatment of early stages of arthritis (La cura tiroidea nelle forme iniziali di artritismo). Baccarani (U.), Rassegna di clin., terap. [etc.] (Roma), 1924, **23**, 1-5.

Obese, plethoric and gouty patients with painful manifestations were treated with "tiroidasi Serono." No results were seen for

about two months, after which improvement set in. A year of such treatment was found to bring about good results.—P. M. N

The thyroid in its relation to the nervous and mental systems. Ball (C. R.), Minnesota Med. (St. Paul), 1922, **5**, 423-426.

This is a brief review of current opinions regarding the nature of thyroid malfunction. The thyroid problem is not one which concerns the thyroid alone, but consists of many morbid processes due to generalized maladjustment. The hyperthyroid type is especially significant of a stigma of constitutional inadequacy.—I. B.

Mitochondria content of the thyroid as an index of the activity of the gland. Bolt (W.), J. Lab. & Clin. M. (St. Louis), 1924, **9**, 630-633.

In 1916 Goetsch reported that the mitochondria of the thyroid are markedly increased in toxic adenomata. Bolt has extended the work by a study of various cases of exophthalmic goiter and of toxic adenomata. In these, Goetsch's findings were confirmed. Of particular interest were Bolt's findings in 6 cases of coloid goiter, in 5 of which toxic symptoms had developed. In one non-toxic case the mitochondria were normal. In 4 of the 5 toxic cases the mitochondrio were augmented. In one of these no other morphologic evidence of toxic activity of the thyroid could be found.—R. G. H.

Influence of iodine on the thyroid (Bemerkungen zur Iodwirkungen auf der Schilddrüse). Breitner (B.), Wien. klin. Wchnschr., 1923, **36**, 603-605.

The thyroid regulates the iodine metabolism of the organism. Breitner considers the colloid as the product prepared by and kept in the thyroid and thinks that when the body needs iodine colloid flows into the blood. Iodine, he states, influences different goiters differently because goiters contain different amounts of colloid. The author believes that in Graves' disease the iodine-protein compound of the thyroid is of inferior quality. Increased activity of the thyroid may be helpful. Small doses of iodine may have a good influence on the iodine-protein compound.—J. K.

Tendon reflexes in myxedema: a valuable aid in diagnosis. Chaney (W. C.), J. Am. M. Ass. (Chicago), 1924, **82**, 2013-2016.

In cases of myxedema, the tendon reflexes produce such slow movement of the parts affected that the quality can be recognized without the aid of mechanical devices and is regarded by Chaney as being a valuable sign in the diagnosis of the disease. In cases of myxedema, a greater stimulation is necessary to elicit a tendon reflex than in a normal person. The period or time interval of a tendon reflex of any person under the same conditions remains the same, and seems independent of the amount of stimulation applied.

In all conditions associated with a low basal metabolic rate studied to date, with the exception of myxedema, the tendon reflexes seem to correspond in every way with those of a normal person. When a patient with myxedema is treated and brought back to normal so that he loses the usual characteristics of this disease, his tendon reflexes also seem to return to normal, and the approach of the reflexes to normal seems to keep pace with the basal metabolic rate.
—Courtesy A. M. A.

Physiology of the thyroid. Charvát (J.), Casop. lék. česk. (Prague), 1924, **63**, 801-805.

Charvát injected intravenously 1 cc. of a 10% solution of sodium iodid per 10 kg. of body weight. The iodin disappeared from the blood faster in hyperthyroidism than in the healthy controls. The blood sugar was not changed or only slightly decreased in normal subjects, while it was increased in hyperthyroidism. It decreased in one patient with exophthalmic goiter who was, however, increasing in weight before the test was applied.
—J. Am. M. Ass., **83**, 78.

Adolescent hyperthyroidism. Cole (W.), Arch. Pediat. (N. Y.), 1923, **40**, 703-707.

A boy 12 years of age, complaining of nervousness, dyspnea, attacks of flushing and loss of weight, improved under the treatment. The boy's mother had a goiter. The treatment consisted of complete rest in bed, low nitrogen diet, light general massage, quinine hydrombromide and sodium bromide.—M. B. G.

The biological test of thyroid substances in blood (Ueber den biologischen Nachweis von Schilddrüsenstoffen im Blut). Csillag (Elisabeth), Arch. f. d. ges. Physiol. (Berl.), 1924, **202**, 588-595.

Eiger's result, that in very great dilution thyroid extracts still increase the action of **adrenin** on the Läwen-Trendelenburg preparation, is confirmed, but the effect cannot be used as a test for the detection of thyroid substances in blood, since blood plasma of normal and of thyroidectomized rabbits, and of normal man and subjects of Graves' disease always itself increases the adrenin action.—A. T. C.

Heart, pulse and blood pressure in exophthalmic goiter (Coure, polso e pressione nel morbo di Flajani-Basedow). Falconcini (R.), Riforma med. (Napoli), 1922, **38**, 465.

A report of 12 cases. There was tachycardia and dilatation of the heart (although not always accentuated in its transverse diameter), arhythmia and extrasystole. The blood pressure was decidedly increased in all cases. The pulse was almost normal except for catacrotism and polygeminism due to extrasystoles.—G. V.

The growth of hair and compensatory hyperplasia of the thyroid after operative removal of incretory glands (Beiträge zur Physiologie der Drüsen. L. Asher. Experimentelle Untersuchungen über den Einfluss der Drüsen mit innerer Sekretion auf die Wachstumsvorgänge, zugleich Beiträge zum Konstitutionsproblem. III.) Furuya (K.), Biochem. Ztschr. (Berl.), 1924, **147**, 425-432.

A normal rabbit regenerates hair within 4 weeks after an experimentally produced defect. When the ovaries are removed this recovery is much less, and when the thyroid is taken out practically no regeneration occurs. The authors believe that they have shown a sex-specific relation between thyroid and gonads in rats and dogs, from the fact that they observed a much greater compensatory hypertrophy or hyperplasia of the thyroid residue in females than in males when one-half was removed. The removal of the testes seemed to exert a retarding effect on residual thyroid tissue enlargement. The number of experiments was very few.—F. S. H.

The rôle of the thyroid in coal-gas and adrenin-glycosuria and hyperglycemia (Untersuchungen über die Rolle der Schilddrüse bein Zustandekommen der Leuchtgas und Adrenalinglykosurie bzw. Hyperglykämie). Geiger (E.), Arch. f. d. ges. Physiol. (Berl.), 1924, **202**, 629-641.

Coal-gas poisoning produces no glycosuria in thyroidectomized dogs; the hyperglycemic curve is the same as that for normal dogs. The absence of glycosuria must therefore be referred to changes of kidney function. Thyroidectomy does not affect the hyperglycemia following adrenin injection.—A. T. C.

Tuberculosis and the endocrine glands. I. The thyroid (Tubercolesi e ghiandole endocrine—Nota 1a: Tiroide). Gelmi (E.), Gior. di clin. med. (Parma), 1924, **5**, 213-221.

Slight hyperthyroidism acts favorably on tuberculosis, but severe hyperthyroidism is harmful. The role of the thyroid in tuberculosis is not yet clearly shown.—P. M. N.

The psycho-electro-tacho-gram (thymogram) and exophthalmic goiter (morbus-basedowi). A contribution to the experimental psychopathology of exophthalmic goiter. Godefroy (J. C. L.), Psychiat. en Neurol. Bl., 1922, No. 3/4, 133-173; abst., Ber. ü. d. ges. Physiol. (Berl.), 1923, **18**, 122.

By connecting a transformer of alternating current the ordinary abducible current of the cutaneous surface (psychogalvanic reflex phenomenon) is transformed into the form of a tachogram. The deviation from the balancing position corresponds to the current variation, thus the deflation forms a plane between the usual curve and that of the tachogram and this corresponds to the amount

of electricity developed by way of a psychogalvanic reaction. The advantage of this transformation lies especially in the fact that it does not approach the height so much as the form of a psychogalvanic current curve. This form stands out rather sharply in a tachogram. The increased affect lability of Graves' disease can be demonstrated in many cases. The Mollsch rotary coil galvanometer was used.—R. G. H.

The effect of thyroparathyroidectomy and parathyroidectomy at 100 days of age on the growth of the brain and spinal cord of male and female albino rats. Hammett (F. S.), J. Comp. Neurol. (Phila.), 1923, **35**, 313-335.

The brain is more dependent on thyroid function for its proper growth and differentiation than is the cord. The growth of the central nervous system is more resistant to the harmful effects of the toxemia induced by parathyroid loss than is that of the body as a whole. The causes of the greater retardation of brain growth, as compared with the growth of the cord, lie in the lesser inherent growth ability of this organ, the high protein-low lipoid composition of the brain as compared with the high lipoid-low protein composition of the cord and the apparent relatively less dependence of lipoid formation and deposition on the anabolic function of the thyroid than is found in cytoplasmically active material. The change induced in the differentiation of brain and cord from the normal, after thyroid loss, is indicative that the growth of the brain is qualitatively as well as quantitatively altered by this procedure. The differences in degree and nature of the changes in differentiation of the brain and cord in conditions of chronic parathyroid deficiency are not sufficient to warrant any definite conclusion as to their significance.—Abst., Wistar Inst.

The growth of the heart, lungs, liver, kidneys, spleen, submaxillary glands and eyeballs in male and female albino rats thyroparathyroidectomized and parathyroidectomized when 100 days of age. Hammett (F. S.), Am. J. Anat. (Phila.), 1923, **32**, 75-94.

The lack of thyroid (thypar) secretion causes an absolute inhibition and retrogression of the growth of the heart, lungs, liver, kidneys and spleen of albino rats of both sexes. The growth of the liver in the females is only retarded. When parathyroid secretion is lacking, simple retardation is shown by the heart, lungs, liver and kidneys. Spleen growth is apparently accelerated. Submaxillary growth is inhibited by thyroparathyroidectomy, while parathyroidectomy is followed by submaxillary enlargement. The growth of the eyeball seems to be quite resistant to thyroid and parathyroid deficiency. The significance of these observations is discussed.

—Abst., Wistar Inst.

The effect of thyroparathyroidectomy and parathyroidectomy at 100 days of age on the Ca, Mg and P content of the ash of the humerus and femur of male and female albino rats. Hammett (F. S.), J. Biol. Chem. (Balt.), 1923, **57**, 285-303.

There is no definitely detectable differentiation in the chemical composition of the humerus and femur of normal rats during the age period from 100 to 150 days. When the thyroid apparatus is removed the ossification ability is decreased. In both bones of both sexes there is a slight shift in the nature of the ash deposited. The direction of this shift is toward a higher percentage of magnesium and phosphorus than the normal. This is believed to be an effect of the parathyroid deficiency since it is shown to a much more marked degree in the parathyroidectomized rats. No change in the percentage of calcium was caused by thyroparathyroidectomy or parathyroidectomy in the male rats. It is therefore clear that although the calcium-retaining ability of the organism is reduced by lack of function of both the thyroid and parathyroid glands the process of calcification is undisturbed. This is evidence that the formation of a bone ash of normal calcium content is not directly related to thyroid or parathyroid function. The ash of both bones of the parathyroidectomized females had a lower percentage of calcium than the normal. The same was true, but to a lesser degree, of the ash of the bones of the thyroparathyroidectomized females. It is therefore probable that the lower calcium found here is to be associated with parathyroid rather than thyroid deficiency. This low calcium in the ash of the bones in the female is possibly attributable to a combination of ovarian and parathyroid deficiency.

—F. S. H.

Post-partum hyperthyroidism (un cas d'hyperthyroïdie des suites de couches). Laffont, Bull. Soc. d'obst. et de gynéc. (Par.), 1923, **12**, 301-302.

Placenta preparation, fed to a primapera to stimulate milk secretion was followed by symptoms of hyperthyroidism which subsided on discontinuing of the medication.—F. S. H.

A consideration of the diseases of the thyroid gland. Mastin (E. V.), South. M. J. (Birmingham), 1924, **17**, 345-349.

This is a brief recapitulation without new material.—J. C. D.

The relation of the function of the thyroid to the amount of nitrogen contained in viscera. Ryu (M.), Nihon Naikagakukai Zasshi (Tokyo), 1923, **2**, 833-868.

The author estimated the quantity of rest nitrogen, urea, ammonia, amino-acid, creatinin and creatin in the liver, kidney, heart, muscle, spleen, and brain of normal, thyroidectomized and thyroid-fed rabbits. The amount of rest nitrogen decreased in the liver, kidney, heart, muscle and brain after removal of the thyroid, while

that of the spleen seemed to be slightly increased. An increase was found in all viscera, except the brain, in the animals fed with thyroid. Urea decreased in the liver, kidney, muscle and brain of the animals with thyroid removed, and increased in several viscera of those fed with thyroid. A slight increase in the amino-acid content of the liver, kidney, heart and muscle was found in both the thyroidectomized and thyroid-fed animals. Ammonia increased in the kidney, heart and spleen, but decreased in the muscle and brain after removal of the thyroid, while it increased in all the viscera on feeding with thyroid. Creatinin increased slightly in the kidney, but it showed no marked change in liver, heart and muscle after removal of the thyroid. A slight increase was found in the kidney, but a decrease in the muscle on feeding thyroid; there was marked change in other viscera. The change in the amount of creatin was very interesting. It decreased in animals with the thyroid removed, but this decrease was much more evident in those fed with thyroid.—K. H.

Experiences in the campaign against goiter among young girls above school age by means of iodine tablets (Erfahrungen über Kropfbekämpfung mittles jodhaltigen Tabletten bei älteren, schulentlassenen Mädchen). Silberschmidt (W.), Schweiz. med. Wchnschr. (Basel), 1923, **53**, 637-639; Bull. mens. office internat. d'hyg. publique, 1923, **15**, 1376.

The author describes the use of chocolate tablets containing 0.5 mg. iodine at the rate of one tablet per week for two years. The results were good with girls from 15 to 21 years of age, but not so good as those with younger children. Silberschmidt advises against too great expectations from the use of iodized table salt, although its use is free from danger. Less satisfactory results are to be expected in relieving goiter among adults than among children.
—Chem. Abst., **18**, 1338.

Bile salt metabolism. II. Proteose and x-ray intoxication. Thyroid and thyroxin. Smyth (F. S.) & Whipple (G. H.), J. Biol. Chem. (Balt.), 1924, **59**, 637-646.

Thyroid extract and thyroxin given to dogs in sufficient dosages to cause an increase in the urinary nitrogen do not modify appreciably the bile salt output under the conditions of the experiments.
—F. S. H.

Results of iodin administration in exophthalmic goiter. Starr (P.) & Means (J. H.), Tr. Am. Soc. Clin. Investigation, 1924.

Patients with exophthalmic goiter have been given by mouth 15 drops of compound solution of iodin daily. Determinations of their basal metabolic rate, pulse and weight were made daily, or at intervals of a few days, for weeks and months. In many cases a

great drop in metabolic rate began soon after iodin was started. Cases with metabolic rates of plus 50 or 60 fell within a few days to plus 10 or 20; others fell to zero or below. This amounted to complete remission of the disease, and is similar to that following subtotal thyroidectomy; the pulse became slow; appetite became normal; nervousness and tremor diminished, and weight increased. We feel that iodin produced this crisis since with a remission in treatment prompt recrudescence of the original disease occurred. Most of our patients were operated on or received roentgen-ray treatment after this drop in metabolic rate, but some that were given iodin for several months had, nevertheless, a gradual recurrence. The primary drop in the out-patients required about a month, in contrast to the immediate drop in the patients at rest in the hospital. After another month the basal metabolic rate increased again, reaching its original toxic level in two more months. The patients were then successfully operated on. Continuance of the iodin probably did not cause the return of the disease, since in those cases in which it was stopped during the recurrence a still greater rise occurred. Certain patients receiving compound solution of iodin and roentgen-ray simultaneously were at normal limits at the end of five months. Another group of subjects, including several with exophthalmic goiter and with toxic adenoma, were apparently unaffected by the administration of iodin. We conclude that large doses of compound solution of iodin by mouth produce abrupt remission in many cases of exophthalmic goiter. The rate of drop is as rapid in these cases as that following subtotal thyroidectomy. Iodin is the effective agent, as its withdrawal is followed by abrupt recurrence of the disease. Iodin alone, as now given, has not been shown to be sufficient to suppress the disease permanently. Iodin and roentgen-ray treatment have been successfully combined in the treatment of some cases. In some cases iodin has no apparent effect.—J. Am. M. Ass., **82**, 1989.

The cardiac disturbances associated with diseases of the thyroid gland. Wilson (F. N.), J. Am. M. Ass. (Chicago), 1924, **82**, 1754-1756.

Most of the cardiac abnormalities produced by thyroid disease occur in those toxic states in which there is an elevation of the basal metabolic rate. So far as the disturbances of the cardiovascular system are concerned, there is little difference between typical exophthalmic goiter and so-called "adenoma with hyperthyroidism." In discussing the cardiac aspects of these conditions, Wilson distinguishes between primary and secondary disturbances of the heart. Under the former heading he includes those cardiac symptoms and signs which occur invariably, or almost invariably, in severe cases of thyrotoxicosis, and which may be considered, therefore, cardinal manifestations of thyroid intoxication. Under

the second heading, on the other hand, he includes those cardiac abnormalities which, because of their relative infrequency, or because their frequency and intensity do not vary directly with the intensity of the other symptoms of the primary disease, may properly be looked on as complications. Of the primary disturbances of the heart, sinus tachycardia and the evidences of overactivity of the heart associated with it are the most common. Of the cardiac complications of thyrotoxicosis, enlargement of the heart is one of the most important. Clinical evidence of myocardial changes in toxic goiter is by no means rare. Death resulting purely from the cardiac complications of toxic goiter is relatively uncommon. It is true that, in so-called postoperative thyroid shock, auricular fibrillation, with extreme ventricular tachycardia and indications of cardiovascular collapse, are seen; but necropsies in such cases usually show severe degenerative changes in the liver and other parenchymatous organs, indicating death from profound toxemia. It is probable that death results in such instances from overwhelming intoxication, in which the heart suffers along with the other vital organs. Milder grades of cardiac weakness are not infrequent, and should be treated exactly as under other circumstances, by rest; morphin when necessary to relieve dyspnea or insure complete rest and sleep; digitalis in amounts sufficient to produce its characteristic effects, and a proper diet. The diet should be designed to meet the caloric requirements, or, perhaps, for the first few days, to fall somewhat below them; it should contain only sufficient protein to prevent a negative nitrogen balance, and should be poor in salt. As to whether adenomatous goiter without hyperthyroidism may damage the heart, it is difficult to form an opinion. Nevertheless, it is clear that a persistent enlargement of the thyroid gland, even though it be regarded as non-toxic at the time of the examination, is at least a potential menace to the myocardium.

—Courtesy A. M. A.

Hydroelectrotherapy in exophthalmic goiter (L'idroelecttroterapia nel gozzo esoftalmico). Vinaj (A.), Riv. di idrol. climatol. e terap. fisiol. (Milano), 1924, 35, 106-110.

This treatment is said to be useful in the early stages of the disorder, whether used in connection with opotherapy or not.

—P. M. N.